FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

EIGHTIETH MEETING

OF THE

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

8:30 a.m.
Friday, February 28, 1997

Jack Masur Auditorium
Building 10, Clinical Center
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland

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C O N T E N T S
MORNING SESSION

NDA 20-689, POSICOR
(mibefradil dihydrochloride) tablets,
to be indicated for hypertension and angina

C O N T E N T S
AFTERNOON SESSION

NDA 20-178, INTEGRILIN (intrifiban)
to be indicated for
adjunct antithrombotic therapy in PTCA

P R O C E E D I N G S

(8:30 a.m.)

DR. MASSIE: I want to welcome you to the continuation of the 80th meeting of the Cardio-Renal Advisory Panel.

We have two more NDAs to review today, and again time will be short, so we'll try to stay on schedule.

Let me start with our reading of the waivers and conflicts of interest of the members of the committee.

MS. STANDAERT: The conflict of interest for February 28, 1997. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. 208(b), full waivers have been granted to Drs. Barry Massie, Lemuel

Moye, and Dr. Robert Califf which permit them to participate in all official matters concerning Posicor.

In addition, Dr. Dan Roden and Dr. Udho Thadani are excluded from participating in all official matters concerning Posicor, but in accordance with 18 U.S.C. 208(b)(3), a limited waiver has been granted to Dr. Udho Thadani. Under the terms of this limited waiver, Dr. Thadani will be allowed to participate in the committee's discussions and deliberations concerning Integrilin; however, he will be excluded from voting with respect to this drug.

Copies of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

We would also like to disclose for the record that Dr. Robert Califf and his employer, the Duke University Medical Center, have interests which do not constitute a financial interest within the meaning of 18 U.S.C. 208(a) but which could create the appearance of a conflict. The agency has determined, notwithstanding these involvements, that the interest of the government in Dr. Califf's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Califf may participate in all

official matters concerning Posicor.

Additionally, Dr. Cindy Grines and Dr. Robert Califf will be excluded from participating in all official matters concerning Integrilin.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

That concludes the conflict of interest statement for February 28, 1997. Thank you.

DR. MASSIE: Thanks, Joan.

In addition to all of that, I wanted to make note of the fact that I was a participant in a study involving mibefradil in hypertension which is not one of the pivotal studies in this trial but through our nonprofit research foundation at the VA, I was a participant, and I see that that was not mentioned in my waiver, but rather some other interests. So, I will continue to participate

in the discussion but will not vote as a result of that.

The agenda this morning starts with the sponsor's presentation, and they've asked -- and I think it's a good idea -- that this presentation will take part in two sections, one of efficacy and one on issues related to safety and electrocardiographic changes. They've asked that the committee ask their questions on the efficacy segment after that presentation, so that will be part-way through. So, we'll take a break, have our discussion on that part, and then move on with the second part.

Without further ado, let's start with this presentation.

MR. LUCEK: Good morning, Dr. Massie, Dr. Temple, Dr. Lipicky, members of the Cardio-Renal Advisory Committee, ladies and gentlemen.

I'm Rudolph Lucek, Group Director, Drug Regulatory Affairs at Hoffmann-La Roche. I'd like to thank the members of the committee for their time in preparing for today's meeting. I'd like to thank the members of the Cardio-Renal Division and particularly Dr. Lipicky for their time and efforts in reviewing this application.

Posicor is the proprietary name for mibefradil dihydrochloride. It is a long-acting, non-dihydropyridine calcium blocker which lowers heart rate without any

negative inotropic effect.

Posicor has been studied for the treatment of hypertension in chronic stable angina pectoris in a worldwide clinical program since 1990.

An NDA for these two indications was filed with the Food and Drug Administration in March of 1996.

Additionally, in a separate program, Posicor is being studied for the use in the treatment of congestive heart failure. This 3-year mortality/morbidity study, the MACH 1 study, is projected to complete in mid-1998.

Today we will present data supporting the efficacy and safety of Posicor for use in the treatment of hypertension in chronic stable angina pectoris.

A comprehensive profile of the drug has been provided to committee members prior to today's meeting in the form of copies of the Cardio-Renal's reviews of the NDA, along with a summary prepared by the sponsor of the drug's toxicology, pharmacology, pharmacokinetics, clinical efficacy, and safety.

Due to time constraints, the FDA has requested that we focus our presentation today on the questions before the committee. We will, therefore, limit our presentation to a brief review of the efficacy and tolerability of Posicor in both hypertension and angina.

This presentation will be made by Dr. Isaac Kobrin, Clinical Research Director. Dr. Kobrin will then focus on the effect of Posicor on cardiac repolarization. In conjunction with this presentation, Dr. Jeremy Ruskin, Director of the Cardiac Arrhythmia Service at Massachusetts General Hospital, will provide an overview of drugs affecting cardiac repolarization, and Dr. Gordon Tomaselli, Associate Professor of Medicine at Johns Hopkins University, will present Posicor's electrophysiologic profile. Dr. Kobrin will then conclude with a clinical discussion of Posicor in cardiac repolarization and a presentation of safety.

We also have with us today representatives from our departments of toxicology, pharmacology, pharmacokinetics, clinical research and statistics who will assist in addressing any questions raised by the committee.

Due to the specialized nature of some of the areas to be discussed today, we are also accompanied by the following consultants who will assist in addressing committee questions and may be called upon by presenters to add comment and clarification. They are: Dr. Denis Noble, Burdon Sanderson Professor of Cardiovascular Physiology, University of Oxford, Oxford, England; Dr. Michael Sanguinetti, Professor of Medicine, Division of Cardiology,

University of Utah; Dr. Suzanne Oparil, Professor of Medicine, University of Alabama at Birmingham; and Dr. Craig Pratt, Professor of Medicine, Baylor College of Medicine, Houston, Texas.

I now would like to turn the meeting over to Dr. Kobrin who will begin with an overview of efficacy and tolerability.

DR. KOBRIN: Mr. Chairman, ladies and gentlemen, as indicated by Mr. Lucek and as we were asked by Dr. Lipicky, we are going to present shortly the preclinical pharmacology of mibefradil, the efficacy and tolerability of the drug in the treatment of hypertension and chronic stable angina pectoris. This is in order to have enough time for presentation and discussion of the main topic of today, mibefradil and cardiac repolarization, looking at preclinical and clinical aspects, and then presenting the safety of the drug.

In the preclinical studies, it was found that mibefradil is a non-dihydropyridine calcium channel blocker. It blocks both L and T-type calcium channels, and the blockade of both channels is highly voltage dependent, and the blockade is selective for T-channels. These two aspects -- the clinical relevance of this is still not certain.

In these preclinical studies, it was found that mibefradil is a peripheral and coronary vasodilator. It has a long duration of action. Its treatment is associated with the reduction of heart rate, and there is no negative inotropism in these preclinical models.

In the clinical NDA, we have studied 5,600 patients and healthy volunteers. Of these, 4,279 patients and healthy volunteers were treated with mibefradil. Today I will mainly concentrate on those who were treated for hypertension and chronic stable angina pectoris.

Half of the patients were studied in the States. The male/female ratio was 2 to 1. 30 percent were elderly, and about 11 percent were African Americans. About 30 percent of the patients were followed for 6 to 12 months, and overall exposure was 1,255 patient-years.

The antihypertensive efficacy of mibefradil was studied in 10 large studies: one open-label long-term safety, and the others controlled studies. Four were placebo-controlled, dose-finding studies, and five were active-controlled studies. In two of them, we implemented a randomized withdrawal versus placebo for 4 weeks, after 12 weeks of treatment in order to evaluate tolerance, rebound, and withdrawal effects.

Among the four placebo-controlled studies, one

was specifically in elderly and one was specifically in patients who were treated with hydrochlorothiazide but their sitting diastolic blood pressure was not lowered below 90 millimeters mercury.

The primary efficacy parameter in all studies was sitting diastolic blood pressure at trough in the intent-to-treat population.

I will mainly concentrate on the results of the placebo-controlled studies, and the main result of the primary efficacy parameter can been seen in the next slide.

Each slide represents the treatment effect, placebo-corrected, and 95 percent confidence interval. When the line is not crossing the 0 line, it is statistically significant with an alpha level of less than 5 percent.

What we can see is that in each of the four placebo-controlled studies, several doses of mibefradil were significantly better than placebo, and there was a significant dose-response relationship across the studies including the elderly patients and patients on hydrochlorothiazide treatment.

Looking at the same data by dose, we see the following. We see the doses on the left side. The 6.25 and 12.5 milligrams were not different from placebo. We

start seeing something with the 25 milligram dose. However, it was not better than placebo in three of the four studies, including high risk populations, elderly patients and patients on hydrochlorothiazide treatment.

A consistent effect can be seen from the 50 milligram onward. The full effect of the drug was achieved within 1 to 2 weeks of treatment and it was achieved gradually.

In addition, treatment with mibefradil was associated with a smooth 24-hour blood pressure control, with a trough/peak ratio of more than 75 percent. This was also confirmed in two studies in which we studied the drug over 24 hours. One study was in-hospital and one study was ambulatory blood pressure monitoring. In both studies, there was a consistent decrease in blood pressure over the 24 hours, including the morning hours, and this is consistent with the high bioavailability and the long half-life of the drug.

There was no tolerance during the treatment with mibefradil, and the effect of the drug was associated with a dose-related decrease in heart rate.

The antianginal efficacy of mibefradil was studied in seven large studies. Five of them were placebo-controlled, two as monotherapy and three on top of chronic

antianginal therapy. In two of them, it was beta-blocker treatment. In one of them, it was long-acting nitrates. In one study, we implemented a randomized withdrawal period of 4 weeks versus placebo after 12 weeks of treatment, again to see if there is any tolerance, rebound, or withdrawal effects.

The parameters that were studied in this study can be seen on this slide. Exercise test parameters. The primary parameter was total exercise duration symptom limited. And we looked at time to onset of angina and time to onset of 1 millimeter ST segment depression during exercise.

Two diary parameters were looked at: weekly anginal episodes and nitroglycerin consumption.

And two parameters of silent ischemia, the number and the duration of silent ischemia, over 48 hours of Holter monitoring.

Looking at the primary parameter of the exercise test, we can see in the next slide the results by study. The first two studies were the dose-finding studies, and there was a significant dose-response relationship. In each one of the five studies, mibefradil was significantly better than placebo in prolonging exercise duration by at least one of two doses.

Looking at the same results by dose in the next slide, we can see the following. The 25 milligram dose was not better than placebo. The 50 milligram dose was significantly better than placebo in three out of five studies. It was significantly better than placebo in three out of three studies, and the 150 milligram was not different from the 100 milligram in prolonging exercise duration.

Looking at the secondary parameters during exercise, time to onset of angina, we see the same pattern: 25 no different from placebo. In two out of the five studies, the 50 milligram was better than placebo, and the 100 and 150 milligram doses were always better than placebo, and there was no difference between these two doses regarding the delay in the time to onset of angina.

The objective parameter among the three, which is time to onset of 1 millimeter ST segment depression, can be seen here. We can see that consistently mibefradil was better than placebo from the 50 milligram onward, and there was no difference between the 100 and 150 milligram doses with regard to the ability to delay the onset of ischemia during exercise.

The diary parameters can be seen in the next slide. Now, each study by itself was not powered to look

at these parameters because many patients did not have anginal attacks when they entered the studies. There was no prerequisite to enter the studies having anginal attacks. Therefore, we did a pooled analysis of these parameters. It was the five placebo-controlled studies.

The results mimic the results of the exercise test. What you can see, again the 25 milligram, no different from placebo, and we see a significant effect with the 50 milligram, a further effect with 100, and no difference between 100 and 150 in reducing the number of anginal attacks per week in these patients, and the same pattern for the decrease in nitroglycerin consumption.

In addition, treatment with mibefradil was not associated with the development of tolerance. There was a dose-related decrease in silent ischemia. There was a dose-related decrease in heart rate, and there was a dose-related decrease in double product both at rest and during exercise.

The tolerability of mibefradil was mainly evaluated in the placebo-controlled studies. We can see in the next slide the most frequent adverse events observed in the placebo-treated patients and mibefradil-treated patients. Here we see all doses of mibefradil, and here a more conservative approach, only the effective doses of

mibefradil.

What we can see, each one of the most frequent adverse events, the difference from placebo was relatively small, and overall the number of patients with at least one adverse event was 29 percent on the placebo group, 35 percent on the all mibefradil, and 38 percent on the effective doses.

Looking at these adverse events by dose on the next slide, we looked at the placebo subtracted for the ease of following these results. At the bottom, we see the incidence of patients having at least one adverse event, and we see that after the 100 milligram dose, the incidence of the difference from placebo was small. We see an increase in the incidence of adverse events with higher doses. When we look at the specific adverse events, we can see that at the 100 milligram dose, the difference from placebo was relatively small. Only when we got to higher doses, we can see that there was an increase in dizziness and leg edema, and we can see headache with the 200 milligram dose.

Regarding dropouts because of adverse events, we can see the most frequent dropouts here on this slide. This is the placebo group, again all doses of mibefradil, no real difference overall, and the effective doses of

mibefradil. We can see that there was no one specific reason for dropouts because of adverse events. Maybe the only one which was different was dizziness which was .7 percent compared to .2 percent.

Looking at other adverse events like myocardial infarction, it was seen on placebo but not on the effective doses of mibefradil in the placebo-controlled studies.

Looking at the dropouts by dose in the next slide, placebo subtracted, we can see that after the 100 milligram dose, the difference from placebo by indication and overall was small. Only when we go to the higher doses, we see more dropouts because of adverse events.

What about treated emergent ECG changes, and I will mainly concentrate on the clinically relevant and the repolarization part will come later on.

You can see on the next slide here the overall incidence was small, so I'm looking here at the whole database of the hypertension and angina. We can see that again after the 100 milligram dose, if you look at 2nd degree AV block, 3rd degree AV block, and sinus node dysfunction defined as pauses on Holter monitoring mainly or brady/tachy arrhythmias, you can see that the incidence was very small. Only when we go again to the higher doses, we see an increase.

Interestingly, most of these events were observed on Holter monitoring at night, mainly a drop of 1 or 2 beats, and most of them, as I said, were asymptomatic. The only 3rd degree AV block case was seen at the 150 milligram, which is above the recommended doses of the drug, and most of these cases of sinus atrial node dysfunction were also seen on Holter monitoring.

So, if we put all these data together, the efficacy and the tolerability, what we recommend is the following. The 50 milligram dose should be the starting dose for both indications.

The 100 milligram dose should be the highest recommended dose for both indications. This is because in angina the 100 and 150 milligram are equally efficacious. And in both indications, there is an increase in the incidence of adverse events at doses above 100 milligram, and this is especially important in hypertensive patients. We want to keep them compliant over a long period of time and indeed, up to the 100 milligram dose, the drug is very well tolerated.

We have done specific studies in elderly patients, as I've shown you, and also in patients with chronic renal failure, and we have seen no difference with regard to the pharmacokinetic characteristics with regard

to the concentration-effect relationship and with regard to the efficacy. Therefore, there is no need for dose adjustment in these populations: elderly patients and patients with chronic renal failure.

At this stage, if there are any questions about the efficacy, tolerability, or any clarifications that you would like to get, I'll be glad to give to you before we go to our main topic of today, which is mibefradil in cardiac repolarization.

DR. MASSIE: Thank you very much.

Why don't we start with our two reviewers. Dr. Weber, do you have any questions?

DR. WEBER: Dr. Kobrin, thank you for moving so quickly through the data. I think we all appreciate the fact that you were so succinct.

But I did just want to know, since later on we may be discussing the relative merits of different antihypertensive treatments, can you recall what percentage of patients had their blood pressures controlled on average on 50 and at 100 milligrams of mibefradil using the usual criteria of control of getting the diastolic below 90 or a fall of 10 millimeters of mercury? Do you recall that?

DR. KOBRIN: Yes. In general, we did some kind of analysis on this aspect, and on the 50 milligram it was

about 50 percent and on the 100 milligram it was 60 to 65 percent, about. But again, this is based on the overall evaluation across the hypertension studies.

DR. WEBER: I know also in the interest of time you didn't discuss the comparative studies, and again we may talk about that later. It may not be necessary. I noticed that again mibefradil beat one or two of the other calcium channel blockers, if I recall correctly, diltiazem, and it was fairly similar to amlodipine.

But in the amlodipine study, do you recall the percentage of patients who got edema on the two treatments? Was there any difference between them?

DR. KOBRIN: Definitely. Indeed, the efficacy part, mibefradil versus amlodipine, was the same, but there was a big difference when it comes to leg edema. There were 33 percent of the patients with leg edema on amlodipine compared to 4 percent on mibefradil.

The efficacy results of the comparative studies -- if you would like, we can show it very briefly, if you would like to see it.

DR. WEBER: Well, maybe we don't need it now, Mr. Chairman. It's more the side effect story that I was interested in.

One last thing. It's a little interesting that

there's a small reduction in heart rate, dose-dependent, which obviously goes with the pharmacology of the drugs. Are there any data in humans concerning whether this drug has any effect on the circulating catacholamines or on the renin-angiotensin system?

DR. KOBRIN: We looked at this aspect in one pharmacology study in healthy volunteers where we didn't see a reflex increase in neurohormones.

In the clinical studies, we have looked at it in one study in patients with congestive heart failure where we didn't see a reflex increase in neurohormones. But I must admit that these were not very well-controlled studies, and in order to look at neurohormones, we need to look at a very specialized center to look into this. But what we have seen, that there is no reflex increase in neurohormones.

DR. MASSIE: John?

DR. DiMARCO: Thank you. Most of my questions will probably come later.

But in looking at the protocols, I noticed that in the hypertension protocols, you excluded all patients on antiarrhythmic drugs. Was that present from the start of the studies, or was it only after the changes on the electrocardiogram were noted?

DR. KOBRIN: We didn't exclude any patient because of this repolarization aspect because we were not aware of any problem with this regard, and generally when we excluded patients, for example, with atrial fibrillation or arrhythmia, it was because it interferes with the ability to measure the blood pressure during the evaluation and it interferes with the objective looking at this aspect. It was mainly done in the initial studies where we wanted to evaluate efficacy.

In later studies, like in the safety study, there was no problem to go into the study with anything, and there was no exclusion because of QT interval or any other things like this.

DR. DiMARCO: Okay, thank you.

DR. LINDENFELD: I have a question on the primary endpoint for the angina component because you gave what appeared to be multiple primary endpoints. According to the materials I have, I guess the primary endpoint is total exercise duration. Is that correct?

DR. KOBRIN: That's right, and this was the only primary parameter.

DR. LINDENFELD: Okay. So, symptoms in the ST depression were not primary endpoints?

DR. KOBRIN: No. It was secondary. Only

exercise duration was primary. All the rest were secondary parameters.

DR. LINDENFELD: And it's 50 seconds difference compared to placebo?

DR. KOBRIN: When you look at the 100 milligram dose, that's correct.

DR. LIPICKY: Barry, excuse me. I might clarify just a little bit on the basis of the question.

Our usual notions are that the treatment of an antianginal is symptomatic relief and that if one can exercise longer until they develop angina, that that's a clear demonstration of being able to affect the symptom, but that in addition to being able to show that, there needs to be able show in that same patient population that the drug is also anti-ischemic, if you will. So, ST segments are measured and time to ST segment and stuff like that, but that is always a secondary kind of measure.

DR. GRINES: Are you going to show us any of the active-controlled trials?

DR. KOBRIN: Active-controlled? If you would like, I can show you. In the angina?

DR. GRINES: Yes. I don't know what the rest of the committee thinks, but it would be helpful to look at those.

DR. KOBRIN: Okay, if we can see carrousel 3, slide number 20 please.

We compared mibefradil to two other antianginal drugs, to diltiazem slow release and to amlodipine.

On the top part, we see the comparison with diltiazem slow release, and the doses were, one, 90 milligrams twice a day, 120 milligrams twice a day, and we used the recommended doses of mibefradil. We can see that compared to diltiazem at these doses, there was no difference between the two drugs with regard to the three exercise test parameters.

However, when it comes to amlodipine, we can see that the effect of mibefradil was significantly larger than the effect of amlodipine at the 10 milligram dose with these p levels and treatment effects, as we can see here.

So, these were the two studies where we compared mibefradil to two other calcium antagonists for the treatment of chronic stable angina pectoris.

DR. MASSIE: Thank you.

Do you have any other questions?

DR. KONSTAM: Can I just ask about that?

The amlodipine in that trial, the scheme for dosing of amlodipine -- did it go up to the 10 milligram dose --

DR. KOBRIN: This was a forced titration study going to 100 milligram mibefradil versus 10 milligram of amlodipine.

DR. KONSTAM: All right, so they went to 10 milligrams of amlodipine unless they had an adverse effect at the lower dose.

DR. KOBRIN: That's right.

DR. MASSIE: Rob?

DR. CALIFF: I missed it in your safety presentation, but could you tell us what the total number of deaths are in all patients treated with mibefradil versus all patients treated with placebo for the entire program?

DR. MASSIE: Let me just ask, do you plan to present that information in the second part?

DR. KOBRIN: This will come in the safety presentation.

DR. MASSIE: Is it all right if we hold off until the safety --

DR. CALIFF: That's fine.

And the only other question would be, are there comparator studies with beta-blockers?

DR. KOBRIN: No, we didn't have comparative studies versus beta-blockers. We had studies on top of

beta-blockers, two studies where we added either mibefradil or placebo on top of beta-blockers.

DR. CALIFF: Is that because you wouldn't intend for this to be used instead of beta-blockers or --

DR. KOBRIN: Excuse me?

DR. CALIFF: I'm just trying to understand the reason why you wouldn't have comparative information.

DR. KOBRIN: We just didn't do a study versus beta-blockers.

DR. LIPICKY: Because we discourage it.

DR. CALIFF: You discourage it.

DR. LIPICKY: Yes. Why do you want it?

DR. CALIFF: Why would I want to know how this drug compared with beta-blockers?

DR. LIPICKY: Correct.

DR. CALIFF: It seems fairly obvious.

(Laughter.)

DR. LIPICKY: Well, then educate me.

DR. CALIFF: Well, you frequently have to make a choice between one form of treatment or the other. Beta-blockers are the most commonly used with the longest experience and the best data for overall health effects.

DR. LIPICKY: Right. So, let's say that a beta-blocker increased exercise duration in the exercise

tolerance trial by 60 seconds and mibefradil increased it by 67. What does that tell you?

DR. CALIFF: That would say that beta-blockers are probably at least as good for angina, and we know about the other health effects. It would be important information.

DR. LIPICKY: I guess I'm not saying it right. Let me back off for a second.

In general, for the approval of a new chemical entity, the guarantee that is given to the public is that this drug is not placebo.

Now, when you get to looking at comparative trials, the problems are very difficult, but let me sort of make it very global. The worse the trial -- that is, the larger the variability and the poorer it's controlled -- the more likely it is that one is going to get a non-difference. So, seeing non-differences is not terribly helpful.

The second component of that is that it isn't just a dose and what it does, but getting at what dose. In fact, the problem sort of is not only what dose but what interval between doses and so on and so forth.

So, the ability to interpret a positive controlled trial, if you would, has a lot of problems

associated with it, and we don't encourage it very much.

DR. GRINES: But why don't we encourage it? It seems to me --

DR. LIPICKY: Well, I just thought I said why. Because we don't know how to interpret it.

DR. GRINES: But if you have a drug that has been shown to save lives or reduce infarction or reduce --

DR. LIPICKY: Where do you see mortality here? This is exercise tolerance, symptomatic relief.

DR. GRINES: But my question is, shouldn't we compare it to a proven drug that has those benefits?

DR. LIPICKY: For what benefit should we compare it?

DR. CALIFF: Well, I think the point you're making -- and I don't want to usurp all the time here with this discussion. The point you're making is you're discouraging comparative trials altogether, and my concern is that to pick a weak competitor and do a comparative trial when there's a stronger competitor may be of some concern. So, I think if comparative trials are going to be done, they should be done against the strongest competitor in the field and not the weakest competitor.

DR. LIPICKY: Well, that's certainly a true statement. The problem is to discover the weak and strong.

How would you hierarchialize the antianginal agents? Which is the most effective?

DR. MASSIE: I think that I understand Ray's point which is, at least for regulatory reasons, you can't make a lot of sense out of those types of trials, nor is the information required for approval. Rob's point I think as a clinician that type of information may be helpful even though it's difficult to interpret with the standards we'd use for regulatory things.

But I think the reason some of these comparative trials are ultimately done is the consumer demands them, and presumably many physicians will want to know.

DR. CALIFF: There's only one regulatory nuance I can think of, and that's to the extent you allow comparator trials in labeling.

DR. LIPICKY: Well, very few times, and in general, a comparative claim, we require two trials that find the same thing. In fact, then the design and the doses and patient characteristics and selection become very major issues because it would be very easy, just for example to give something that is intuitively clear, to compare a ACE inhibitor to a calcium channel blocker in blacks. You obviously would find a big difference and come

to a different inference if you wanted to draw a conclusion about the drug as opposed to the disease and the characteristics of the patients who have the disease. So, you get into real troubles when you start getting into those comparative situations.

DR. CALIFF: As long as it's clear that the data on the comparative trials is not going to be used for us to go in the labeling, then I don't feel the need to continue the discussion. If it was going to be a labeling issue, then --

DR. LIPICKY: That is correct. These trials will get labeling that will say it behaves like others.

DR. MASSIE: I think those are very important issues, but we'll move on.

John, did you have any more comments?

DR. DiMARCO: No.

DR. LINDENFELD: I notice sinus bradycardia was excluded in every study. Is that correct?

DR. KOBRIN: Excuse me?

DR. LINDENFELD: Sinus bradycardia was excluded in every hypertension and angina study. Is that correct?

DR. KOBRIN: We excluded only patients who had a heart rate below in 55 in most studies or below 50 in some studies.

DR. LINDENFELD: And then heart block, including first degree AV block, that was excluded.

DR. KOBRIN: First degree AV block was not an excluded criteria in most studies.

DR. LINDENFELD: Well, in some of the angina studies here, for instance, 14509, first degree AV block was excluded.

DR. KOBRIN: That's right.

DR. LINDENFELD: I just wondered what percentage --

DR. KOBRIN: That's right. In this study we exclude them, but in other studies we did not exclude first degree AV block. And the overall first degree AV block was found to be dose-related and the incidence was about 4 percent with the 50 milligram dose and 8 percent with the 100 milligram dose.

DR. LINDENFELD: And in the studies in which first degree AV block was not excluded, what was the incidence?

DR. KOBRIN: This is the incidence --

DR. LINDENFELD: Or the incidence of second degree AV block. Do we know that?

DR. KOBRIN: This is the incidence in the studies where it was not excluded.

DR. LINDENFELD: But what about the patients who already had first degree AV block?

DR. KOBRIN: Who already had first degree?

DR. LINDENFELD: Yes.

DR. KOBRIN: They did not progress into second degree, if this is the question.

DR. LINDENFELD: Okay. None?

DR. KOBRIN: No, they did not.

DR. LINDENFELD: Do you know how many patients that was approximately?

DR. KOBRIN: No, I don't have the number.

DR. CALIFF: Barry, I have one more.

DR. MASSIE: Let me get Marv's.

DR. KONSTAM: You know, I'm just interested in driving home in my mind the benefit of the drug over and above beta-blockers. The one study I guess that I'm most interested in is 14446 which showed the clear-cut efficacy at the 100 milligram dose over a beta-blocker. Could you just spend a minute and review the specifics of that in terms of what beta-blocker and what dose and how that study was conducted?

DR. KOBRIN: If I can see carrousel 3, slide 29, and then I will proceed to 30 and 31 to show this data.

Here we can see the effect of mibefradil on top

of beta-blockers in the two studies where it was given on top of beta-blockers. This is the 509 study and this is the 446. What we see is that the 50 milligram in both studies was significantly better than placebo in improving exercise duration and further effect with the 100.

And you see here the 446 study that you mentioned. You see here the ability to delay the onset of ischemia, again the 50 milligram significantly better than placebo in both studies, and the 100 milligram even further effect.

Looking what beta-blockers we were using, the next slide, if we can see. You can see here what beta-blockers were used in the two studies and the percentages. The two studies were done in two different parts of the world. This study was done in Europe and this study was done in the States, so there are some differences with regard to the use of the different beta-blockers. We can see the different percentages. Overall across the groups, it was similar distribution of the different beta-blockers.

The next slide, if we can see, we can see the doses that were used for the different drugs and the different doses of mibefradil, and we can see that overall the use of these drugs was the usual use that we are seeing on the daily treatment of patients with angina pectoris.

DR. GRINES: Do you have any heart rate information on these trials? Heart rate before and after starting --

DR. KOBRIN: Yes. It's interesting that we looked at the heart rate in these studies on top of beta-blockers as compared to studies without beta-blockers, and the difference in heart rate was similar with and without beta-blockers and the amount of decrease with the 50 milligram was about 4 beats per minute -- 4 to 5 -- and with the 100 milligram it was about 8 to 10 beats per minute further decrease from baseline.

DR. GRINES: So, should we interpret that by saying that these patients were not adequately beta-blocked?

DR. KOBRIN: No. It's hard to say if they were not. The average heart rate of the patients on the beta-blockers in these two studies was about 60 to 65 beats per minute, and the usual heart rate in the other studies was about 70 to 75 beats per minute. Some of them definitely were not completely beta-blocked and some of them were beta-blocked, but we have to remember that patients with a heart rate below 55 were not allowed into these studies.

DR. LIPICKY: You may be trying to spin a story that might be spinnable, but the intent of these trials is

to answer the question, does mibefradil beat placebo when there is a background therapy?

These trials were not designed to answer the question, does mibefradil have a bigger effect than a beta-blocker, or does a beta-blocker and mibefradil have a bigger effect than either a beta-blocker alone or mibefradil alone? Those would require studies of entirely different design.

These trials only say that with a background of antianginal therapy mibefradil can be differentiated from placebo. And I think if you try to spin a story bigger than that, I don't think you can.

DR. CALIFF: I just had two other areas I wanted to probe just a little bit.

On the adverse events, dizziness and hypotension. In terms of the specific cases, I know you've looked at those in detail. Those were not rhythm disturbance related, or do you have blood pressures to go with those symptoms? Do you have an explanation for the --

DR. KOBRIN: Let me show you the results that we've seen on the dizziness regarding by dose. If we can look at carrousel 5, slide number 36, we can see what happened to dizziness across the populations that we have studied.

This is the placebo-subtracted incidence of -- we took together dizziness and light-headedness to be more conservative. We can see that it was, indeed, a dose-related increase, but again up to the 100 milligram, the placebo-subtracted was low. Most of these cases did not have any changes in blood pressure regarding, for example, hypotension or postural hypotension. This was a complaint that they had, and again the incidence after the highest recommended dose of the drug, placebo-subtracted, was low.

Regarding postural hypotension and hypotension of first-dose effect, we didn't have this problem. In fact, the incidence was sightly higher on placebo as compared to mibefradil regarding these two adverse events.

DR. CALIFF: And then the second question is your recommendation about renal dysfunction and age. How confident are you in your recommendation that there needs to be no dose adjustment?

DR. KOBRIN: I'm pretty confident because we did specific studies in these patients, one study that I've shown you, the placebo-controlled study dose-finding in elderly patients where the dose response and the efficacy was the same as in non-elderly. The pharmacokinetic characteristics were exactly the same as in the non-elderly, and the concentration-effect relationships were

the same.

We had a specific study in patients with chronic renal failure complicated by systemic hypertension where we compared mibefradil to nifedipine slow release, and in this study the efficacy was similar to what we have seen in studies in patients without chronic renal failure. The concentration-effect relationship was the same.

And we also had a pharmacology study where we looked at pharmacokinetics in patients with renal failure, and there was no difference when you had renal failure and when you didn't have renal failure.

DR. MASSIE: Just one follow-up. I noticed, at least in one of your slides, that most of the people you defined as elderly were in the 65 to 75 range.

DR. KOBRIN: 65 and higher. We also had about 10 percent of the patients, 75 and higher.

DR. MASSIE: Amongst those that went through the pharmacokinetic study you just mentioned, how many of those were over 75?

DR. KOBRIN: The elderly pharmacokinetics was evaluated as population kinetics in the specific study in the elderly. It was a population kinetic evaluation. If you would like, we can show you how it was done, but this was a special approach. It was not just a pharmacology

study. It was a population kinetic approach.

DR. MASSIE: Well, maybe the answer I'm looking for is in terms of your comments about how everything was identical in the elderly as in younger patients, does that hold up for the subset of elderly that are over 75?

DR. KOBRIN: I think it is. Yes. Our pharmacokineticist is saying yes.

DR. MASSIE: So, an 80-year-old is no different than a 60-year-old or a 40-year-old.

DR. KOBRIN: We didn't look at 6 years old.

DR. MASSIE: 60.

DR. KOBRIN: 60.

(Laughter.)

DR. KOBRIN: No. As I know it, and again I'm looking at our pharmacokineticist. He is saying that it was the same.

DR. MASSIE: Yes. I think that's the way I saw the data in the book as well.

All right. Let's move on to the next.

DR. KOBRIN: During the review --

DR. MASSIE: No. I'm sorry. One of our FDA reviewers.

DR. CHEN: Shaw Chen, FDA reviewer. I just have two quick comments.

First is for angina, the 50 milligram dose only works when you have a beta-blocker on board. For monotherapy, 50 milligrams didn't work.

The second comment is I want to also answer Dr. Weber's earlier question that for response rate in hypertension, if you subtract the response to placebo, the 50 milligram response rate is about 20 to 30 percent, and for 100 milligrams it's about 40 to 50 percent.

DR. WEBER: That's after placebo subtracted?

DR. CHEN: That's correct.

DR. MASSIE: That's a little different from the slides that we saw. Was that also your reading of the data, the way Dr. Chen just mentioned?

DR. KOBRIN: You are talking about the --

DR. MASSIE: In angina, if you didn't have the beta-blocker background, there was no significant effect of the 50 milligram dose?

DR. KOBRIN: That is correct. In the two studies where we had monotherapy, the 50 milligram was not significantly better than placebo. It was significantly better than placebo as an anti-ischemic effect in these two studies. Also when we looked, as a monotherapy, when we compared the 50 milligram dose to other comparators, for example, as a monotherapy, it was as effective as 90

milligram twice a day diltiazem and as effective as 10 milligram amlodipine as monotherapy.

Definitely I think that what it shows, that some patients will respond to the 50 milligram as monotherapy on top of what we have seen on placebo, and this is in fact the way the regulation is regarded what will be the starting dose.

Overall in three out of five studies -- and indeed, these were the three studies on top of background therapy -- the 50 milligram was significantly better than placebo.

DR. MASSIE: Any comments?

(No response.)

DR. MASSIE: Let's move on.

DR. KOBRIN: During the review of the NDA studies, it was observed that in one study, in one treatment group a slight increase in QTc interval was observed. Let me show you where it was seen.

What we see here is the placebo-controlled studies, the change from baseline in QTc interval and the 95 percent confidence interval. We see the placebo groups, the 50 milligram groups, 100 milligram groups, 150 milligram groups.

We can see that up to the 150 milligram the

variability and the effects were either similar, lower than baseline, and the only time that there was an increase in QTc was with the 200 milligram dose.

Because of this observation, the FDA raised the concern that this drug might be associated with an increase in QTc and therefore might carry with it a proarrhythmic risk.

We reevaluated our whole database, preclinical and clinical, in order to look into this issue. We performed additional studies, preclinical and clinical, in order to evaluate comprehensively this aspect and see really if there is any concern.

What we have found and what we are going to show you in our data, the treatment with mibefradil was not associated with an increase in QTc. It was associated with a change in the morphology of the T-U wave, and there was no evidence for proarrhythmic risk.

However, before I will show you the data itself, we asked Professor Ruskin to tell us what is really seen when you give drugs that prolong QT and are associated with arrhythmic effects. This is in order to be able to put in perspective what we have seen with our drug, and as you will see later on after this presentation, all the effects of mibefradil are completely different from the

drugs that adversely affect the QT interval. And I would like Dr. Ruskin to give his presentation.

DR. RUSKIN: Thank you, Dr. Kobrin. I appreciate the academic promotion.

(Laughter.)

DR. RUSKIN: Dr. Massie, members of the committee, ladies and gentlemen, the purpose of my comments is to provide a very brief introduction to presentations on the electrophysiologic effects of mibefradil and the electrocardiographic changes seen with the drug.

It's well known to everyone that drugs which are known to cause torsades are generally associated with prolongation of the QT interval, and at the cellular level, that these drugs are associated with prolongation of action potential duration. In fact, the cardinal feature of drugs which cause torsades in patients is prolongation of action potential duration, and this is typically most marked at slow heart rates.

At the level of the intact heart, this prolongation of action potential duration is associated with prolongation of the effective refractory period in the ventricle -- and we're talking here about ventricle as well -- and at the electrocardiographic level, generally with prolongation of the QT interval.

This effect on action potential duration is mediated most commonly by a blockade of repolarizing potassium currents, most commonly IKr, and this can be seen with a wide range of drugs, including class I and class III antiarrhythmic agents, bepridil, erythromycin, terfenadine, astemizole, cisapride, and many other drugs.

Other mechanisms, including stimulation of inward calcium and sodium currents, have also been proposed as potential mechanisms of drug-mediated torsades, but it should be emphasized that all of these mechanisms are associated with prolongation of the action potential duration.

This slide summarizes briefly the effects of four agents from different classes that are commonly associated with the occurrence of torsades in patients with those of mibefradil.

The point that I want to emphasize is purely this one, and that is drugs like sotalol, terfenadine, astemizole, bepridil, and all other agents that have been shown to cause torsades are associated with prolongation of action potential duration in ventricular muscle. These drugs may cause early-after depolarizations and polymorphic ventricular tachycardia in experimental models, but I think that the critical feature is this electrophysiologic

observation.

In contrast, mibefradil either has no effect or shortens action potential duration, and it does this at all concentrations in all preparations and at all stimulation frequencies. In addition, in the models that have been tested, the drug does not cause early-after depolarizations and has not been shown to cause polymorphic ventricular tachycardia.

This slide summarizes the clinical electrophysiologic effects of three agents commonly known to cause torsades with those of mibefradil in patients undergoing electrophysiologic testing, and these are selected data points that reflect effects on effective refractory periods in atrial muscle and ventricular muscle.

Notice that quinidine, sotalol, and bepridil, all associated with torsades, and in keeping with their effects in prolonging action potential duration, prolong effective refractory periods in atrial muscle and in ventricular muscle, whereas mibefradil, which does not affect or shorten action potential duration, has no measurable affect on atrial muscle or ventricular muscle refractoriness.

This slide compares the effects of four calcium channel blocking agents on clinical electrophysiologic

properties also in patients undergoing electrophysiologic studies. Most of these drugs prolong corrected sinus node recovery time and, not surprisingly, they all prolong refractoriness within the AV node.

Notice, however, that diltiazem, verapamil, and mibefradil have no effect on refractory periods in atrial muscle and no effect on refractory periods in ventricular muscle, again in keeping with their lack of effect on action potential duration, whereas bepridil, a drug known to prolong action potential duration and known to cause torsades, increases very significantly refractory periods in the right atrium and in the right ventricle.

DR. MASSIE: Jeremy, I hate to interrupt you, but I wonder if you could just tell us the doses that were being used when those things --

DR. RUSKIN: I don't have those at my fingertips. What I can tell you is that the doses of mibefradil in this study achieved relatively low levels; that is, the goal was to achieve peak levels comparable to the 50 and 100 milligram doses, and those were not achieved. They tended to be closer to trough levels, but they were at levels that achieved significant effect, albeit it small, but significant effect on the AV node. I can't tell you the doses of these other drugs. I'm sorry.

This slide just summarizes for you the fact that both diltiazem and verapamil in extensive experience in large numbers of patients over long periods of time have never been shown to cause torsades in the clinical setting. Bepridil, on the other hand, was well known to cause torsades and documentation of this effect in large numbers of patients was known quite early on in the development of the drug.

Mibefradil in a much smaller population over a much shorter period of time has also never been shown as a single agent to cause torsades. There is one case of torsades in the angina database in a patient who was also taking cisapride.

One final comment about mechanism and that is in recent years at least two different animal models have suggested that torsades may, under some conditions, be related to the occurrence of reentry and that this reentry may be mediated by dispersion of refractory periods across the wall primarily of the left ventricle.

To examine this issue, a study in a canine model was performed measuring the dispersion of monophasic action potential durations across the wall of the left ventricle, and the observations for three drugs are shown here. With sotalol and astemizole a significant increase

in dispersion of monophasic action potential duration was observed, as was the occurrence of polymorphic ventricular tachycardia in this model; whereas, with mibefradil no change in dispersion was observed and polymorphic VT was not observed.

This is my last slide and I show it just to reemphasize the cardinal feature of agents which cause torsades in the clinic and that is prolongation of action potential duration and in general prolongation of the effective refractory period both in ventricular muscle.

It's important to keep in mind that mibefradil does neither of these, and I think that fact is in keeping with its lack of effect both in the preclinical database and in the clinical electrophysiologic study, its similarity to verapamil and diltiazem with regard to its electrophysiologic effects as well. These observations will be important as we begin to look at the electrocardiographic changes, the morphologic changes in the T-wave and the U-wave that are observed with this drug.

DR. KOBRIN: We will continue with the preclinical data with Dr. Tomaselli.

DR. TOMASELLI: Thank you, Dr. Kobrin, Dr. Ruskin, and members of the panel.

As has been alluded to already by both Dr.

Ruskin and Dr. Kobrin, there are morphologic changes in the electrocardiogram observed with mibefradil, and the sponsor has asked me to summarize the preclinical program which was motivated by these morphologic changes.

The components of this program are on this slide, and they are to study the morphologic changes on the electrocardiogram in experimental animals, to study the effect of mibefradil on cardiac action potentials, and to also critically examine the effect of the drug in animal models of arrhythmia.

Now, there were three methodologic principles that were always adhered to in the design of these studies, and they included the use of up to high doses of the drug, and in fact in in vitro studies up to cytolytic concentrations of the drug, the use of high doses of the drug in vivo up to toxic concentrations, and scrupulous attention to the use of the appropriate controls.

This is a slide which shows the electrocardiographic changes observed in conscious squirrel monkeys after being given a high dose of mibefradil. It serves to underscore the motivation for the preclinical program, and it illustrates the typical electrocardiographic changes seen. They include a depression in the amplitude of the T-wave, sometimes with a

notch. This may be the result of an increase in the amplitude of the U-wave, with the movement of that wave closer in the cardiac cycle.

I should emphasize that similar, comparable suprapharmacologic doses of other calcium channel blockers like verapamil produce nearly identical changes in the electrocardiogram.

Well, in order to try to better understand what this electrocardiographic phenomenon means, mibefradil was studied at the cellular, at the intact heart, and at the intact animal level, and I'd just like to share that data with you.

First, in terms of the effect of the drug on the cardiac action potential, without exception the drug produces shortening of the ventricular action potential both in cellular models -- and this is again at high doses, up to cytolytic concentrations of the drug -- in isolated heart models, and in whole animal models, again up to toxic concentrations. Toxicity limitations here were generally due to AV block.

In addition, the drug produced no significant change in the action potential duration rate relationship.

Mibefradil was studied specifically in guinea pig ventricular action potentials and the parent drug and

eight of its direct metabolites produced reversible action potential shortening, again up to high concentrations of the drug. This effect occurred promptly with exposure of the cells to the compound, and there was no further change in either action potential duration or action potential profile with prolonged application of the drug. Also significantly, mibefradil did not antagonize the action potential shortening effect of other calcium channel blockers.

Let me just show you a few cardiac action potentials. These are measured in guinea pig ventricular myocytes at room temperature at a stimulation frequency of 0.6 hertz, although similar data have been obtained at 35 degrees Centigrade as well.

Mibefradil at 10 micromolar. This is a concentration that's three orders of magnitude greater than that observed in man -- free plasma concentration than that observed in man on therapeutic doses. This produces a fairly substantial action potential shortening of about 50 to 60 percent. This effect of mibefradil is very similar to the effect of other calcium channel blockers in terms of the extent of action potential shortening.

This dose-response curve serves to emphasize that mibefradil produces dose-dependent, monotonic decrease

in action potential duration at all concentrations studied with an IC50 of approximately 90 nanomolar. The drug was studied fairly extensively at low concentrations in the picomolar and subnanomolar range, and the drug had no effect on action potential duration and certainly did not prolong action potential duration at these low concentrations.

In addition, a mixture of the drug and its main metabolites in a concentration ratio that was designed to mimic the concentration ratios of the parent drug and its metabolites in man at therapeutic concentrations had no significantly different effect on the action potential duration than the parent drug alone.

This should be held in stark contrast to other drugs which have been associated with QT prolongation and a significant incidence of serious ventricular proarrhythmia. Shown on this slide are quinidine, terfenadine, and mibefradil.

Quinidine at high concentration, 20 micromolar, a dose that is known in vitro to block calcium channels, produces substantial prolongation of action potential duration.

Terfenadine at nanomolar concentrations does the same thing: prolongation of action potential duration.

In contrast, mibefradil again at all concentrations, both low and high, produces action potential shortening.

Similarly, in human myocytes, as illustrated by this human atrial action potential, again recorded at room temperature and similar stimulation frequency, mibefradil at a concentration of 1 micromolar depresses the plateau of the action potential, therefore shortening the action potential duration at 50 percent repolarization, but not changing the action potential duration at all at 90 percent repolarization.

Well, the other main component that governs how long the action potential is are potassium channels. The drug was studied in potassium channels and the results of those studies are kind of emblematically represented in this slide which is a bar plot of the effect of mibefradil on one of the major repolarizing potassium currents in the heart, the delayed rectifier potassium current, the rapid component of that, the so-called IKr, which genetically is encoded by a gene called HERG.

Now, these currents were studied either in mouse tumor AT-1 cells -- and the IC50 for these data points are plotted in the orange bars -- or the block of the HERG current expressed in percent of oocytes by 10

micromolar concentrations of each of these drugs is shown in the yellow bar. The taller the bar, the more potent the block. So, again, mibefradil is studied in the context of a variety of other drugs, some of which have significant action potential prolongation effects and significant proarrhythmic potential.

What I should emphasize here is that mibefradil blocks these currents with an IC50 of .75 micromolar. This is 80 times the predicted free plasma concentration of the drug in patients on therapeutic doses.

Also it's important to notice that the effect of mibefradil on these currents is very similar to other drugs which we know don't cause torsades, like verapamil, amlodipine, propranolol, and captopril.

The effect of mibefradil on the action potential duration-rate relationship is shown on this slide. These data were performed at 35 degrees in the isolated rabbit heart. The action potential duration measured at repolarization over a range of cycle lengths was studied at two concentrations of mibefradil, and at both .1 and 1 micromolar there was no significant change in the action potential duration at any pacing cycle length. In contrast, quinidine between doses of 1 and 10 micromolar produced dramatic prolongation of action potential duration

at all cycle lengths, save for the shortest of cycle lengths.

In addition, the drug was studied in a canine model. This is a canine model where endocardial monophasic action potentials as well as monophasic action potentials across the wall of the heart were measured, and again at 35 degrees over a range of concentrations of the drug, mibefradil produces no significant change in the endocardial monophasic action potential duration. In contrast, the d-sotalol and astemizole produce a dose-dependent increase in endocardial monophasic action potential duration.

Now, as you heard from Dr. Ruskin, prolongation of the action potential duration may not be sufficient to produce a repolarization-induced abnormal arrhythmia like torsades de pointes, and probably dispersion is an important component.

In fact, in this model the sponsor has been able to measure the dispersion across the left ventricular wall of these dogs, again over the same drug concentration range, and what is seen is that mibefradil produces very little change in the dispersion of action potential duration. This is measured as the maximal minus the minimal action potential duration at four sites measured

across the left ventricular wall.

In contrast, both sotalol and astemizole, both of which produce torsades de pointes, produced dramatic increases in dispersion of repolarization.

Well, this drug has been studied extensively in in vivo arrhythmia models. In 13 models of cardiac ischemia, mibefradil prevents serious ventricular arrhythmias in a manner that's very similar to other calcium channel antagonists.

In a canine model of programmed electrical stimulation induced arrhythmia, not surprisingly the drug is inactive.

The drug has also been studied in three in vivo models of torsades de pointes, and I should point out that drugs which prolong the QT interval and have a tendency to produce polymorphic VT, or torsades de pointes, will generally produce that arrhythmia in one or more of these models.

The effect of mibefradil in a cesium chloride canine model is shown on this slide, and it really is representative of all three models studied. So, let me share the data here with you for just a moment.

Mibefradil at 30 micrograms per kilogram per minute reduces the induces the incidence of ventricular

bigeminy. It reduces the incidence of sustained ventricular tachycardia, and it doesn't affect the incidence of non-sustained VT. But importantly, no animal in this study developed polymorphic VT or ventricular fibrillation.

Again, this is in contrast to sotalol which seems to prevent the less serious of the ventricular arrhythmias, but results in an increase in all three of the more serious arrhythmias induced in this model.

In the rabbit torsades model, described by Carlsson and coworkers, sotalol produces torsades de pointes, or polymorphic VT, in roughly half of the animals. When the animal is treated with mibefradil, that completely eliminates the incidence of torsades in this particular model.

Finally, there's a canine bradycardia model of torsades de pointes that was studied. Again, drugs that have clinically been associated with torsades, or polymorphic VT, in over 50 percent of animals produce torsades in this animal model, and again mibefradil appears to be in this model completely protective.

Well, I'd just like to close by summarizing the effect of mibefradil on cardiac repolarization, and I think this can be summarized in three short comments.

First, like in humans at high dose, there are certainly T-U morphologic changes which are observed with mibefradil. These are not unlike the changes observed with verapamil and diltiazem.

Uniformly this drug either, at low dose, has no effect on action potential duration or reduces the action potential duration, again an effect that is very similar to other calcium channel antagonists.

Importantly, mibefradil either results in no change or a decreased incidence of torsades de pointes in relevant animal models of this arrhythmia.

Now, the mechanism by which these T-U morphologic changes is produced is really unknown and is probably multifactorial, although the action potential changes that are observed with mibefradil are not inconsistent with the T-U morphologic changes seen on the electrocardiogram. Professor Denis Noble's group has done an elegant computer simulation to demonstrate that for us, and later in the presentation, if the panel so desires, that data can be shown.

Thank you.

DR. KOBRIN: So, as we have seen from the preclinical studies, mibefradil is associated with a decrease in the myocardial action potential. There are

morphological changes which are similar to those seen with verapamil, and there is no evidence for proarrhythmic effects.

We collected a lot of ECGs from patients treated with mibefradil. We reviewed the whole database to see what is going on in the human database, and what we have seen is the following.

We have seen that there are two processes: one, a decrease in QTc interval, and the other one is the dose-related increase in the incidence of T-U morphological changes.

Now, the incidence of these morphological changes was low at the recommended doses, and it was easy to measure the QTc by the ECG machine and by humans. Indeed, at this level of doses, there was no concentration-related increase in QTc, and I will show you data about it. In fact, there was a decrease in mean QTc interval at the recommended doses, and I will show you the data about this phenomenon.

At supratherapeutic doses, there was an increased incidence of morphological changes that interfered with the ability of the ECG and human to measure the QT interval resulting in an apparent increase in QTc interval. As you will see, these similar morphological

changes were seen with verapamil and diltiazem.

Now, before we show you the data with the recommended doses, let me show you what do we mean by morphological changes in the human electrocardiogram in order that we will see things in the same way.

On this sketch we see the normal electrocardiogram where we can measure clearly the QT, and if there is a U-wave, the Q-U. If there is a morphological change -- and generally we will see a decrease in the amplitude of the T, an increase in the amplitude of the U, and sometimes an increase in the T-U junction -- we can see different kinds of ways of T-U patterns which might result in measurement of QU instead of QT. We can always see the transition between the T and the U.

Now, let's look at specific electrocardiograms and see what we are talking about. This is one case of mibefradil-treated patients where we can see the baseline on L2 and on V3. We can clearly see a small U-wave at baseline. We can see that the QT can be measured clearly on both places, and this is ECG reading QT interval.

All treatment at week 1 with the 200 milligram dose which is twice the highest recommended dose of the drug. We see this morphological change. There is a flattening of the T at week 1 and at week 4, and we can see

the T and the U. In fact, if we look at the QU from baseline to end of treatment, despite the decrease in heart rate, the difference stays the same. In fact, the QUc decreased. And we can see that the tip of the T-wave did not change. The ECG machine couldn't read the limb leads and it couldn't know what to do with the precordial leads.

Another case we can see here. The same thing. We can see a small U-wave at baseline at V2 and V5. We can see that at week 1 there was a rising U-wave here and here. Interestingly enough, at week 4 the changes almost disappear. So, these are changes that come and go, and we can see again if we measured the Q-U interval, we will see that despite the large decrease in heart rate, the change was small, indicating that the QUc in fact decreased.

Now, when we saw these changes with these doses, we said, well, is this unique to mibefradil? And we decided to look what happens with verapamil and diltiazem in healthy volunteers, and we picked these drugs because they are calcium antagonists and because we know that they are not proarrhytmic drugs. Let me show you what we have seen.

This is one case on verapamil and we see this was treated with 240 milligrams 3 times a day. We can see the baseline. We can see how the T-wave disappeared at day

7, and at day 9 we get a kind of a T-U complex. This is very clear what we see here with verapamil.

In another case where we gave verapamil twice recommended doses, the same as we gave mibefradil twice recommended doses, this is what you get. Baseline, day 9, and day 14. Definitely the machine doesn't know how to deal with these. It reads it as a long QTc. If we look at this, we have the T and the U, we have the T and the U, and this is the T-U complex. These changes are similar to what we have seen with mibefradil at twice the recommended doses of the drug.

What about diltiazem? This is one case of diltiazem given at the beginning at 360 milligrams once a day, and we can see that the T-wave disappeared almost, flattened. When we look at the strip comparing baseline and 360 milligrams three times a day, we can see the rising U-wave, the merge of the T and the U, and the T-U complex with diltiazem.

We can see another case. The same thing, giving 360 milligrams three times a day. The T-wave disappeared and we see the T-U complex as compared to baseline. We can see if one would measure here QU or QT, it's very difficult to find where it is. But if you compare QT to QU, you might find out that there is an

increase in QT, but in fact it's an apparent increase in QT. It's not a real one because we compare here QT with QU, and we see that here we hardly see any difference between the T and the U-wave when we give diltiazem treatment.

So, definitely what we see here with mibefradil, verapamil, and diltiazem, morphological changes of the T-U wave which are similar which may result in an apparent increase in QTc at high doses. I'm saying apparent. Let me give you just one example what do I mean.

We treated 6 healthy volunteers with 250 milligrams of mibefradil, which is two and a half times the recommended doses. In all 6 healthy volunteers, we had U-wave at baseline. Let me follow this slide.

This is the baseline of these 6 healthy volunteers. This was the QTc and this is the QUc. We had a very clear U-wave in all 6 healthy volunteers.

On active treatment, there were changes in morphological change and the QU was this, and overall a decrease from 571 to 550.

Now, in two cases one could not measure the QT because of this morphological change. Now, if we will replace the QT by QU, one would get an apparent increase in QTc from 362 to 433. If one would take only the four cases

where we can measure the QT, there was no change or even a decrease.

This is what we mean by apparent increase in QTc and this is what happened at the 200 milligram dose.

Now, we spent many hours looking at these ECGs together with Dr. Lipicky, and at this moment I would like to ask Dr. Lipicky to share with us what we have seen together.

DR. RAEHL: One quick question. Was that last study a chronic dose or a single dose?

DR. KOBRIN: This one? Once a day, 250 milligrams once a day.

DR. LIPICKY: How many weeks?

DR. KOBRIN: It was between 10 days -- you're talking about the mibefradil, the apparent increase? It was between 10 days to 24 days, the length of the treatment.

DR. LIPICKY: If you could put the FDA carrousel in and go to slide 29.

So, indeed, we looked at cardiograms, and we did the usual things: measured the PR, the QT, the QU, and sort of general morphology. I think that there were something on the order of 120 cardiograms or something that came, and after having gone through only 38 of them, I

decided that there was no further utility in our looking at them together.

So, what I want to do is to show you part of what was seen and what is hard to do and what I was trying to do when looking at these cardiograms is to give the Gestalt of what you see because whenever you select patients, you can clearly select what you want to see and it can look like a pretty good story. I want to say that I may not be able to do that because it's hard to do. What I want to make clear is that this is sort of typical, if you would, and it isn't highly selected.

So, what's shown on this graph is the 6 normal volunteers that were just alluded to who received 250 milligrams. There will be two other slides that are like this where each bar or big bar is a patient, and within each patient is a measurement of QT, the sort of pale thing in green, and a measurement of QU, the pink and yellow, before and after drug that was administered once a day for several days at least and oftentimes for as long as 4 weeks.

What you generally see in this set of cardiograms is that where you can measure a QU or a QT, before and after treatment, there is no change.

This is a set of patients who got to be looked

at because they appeared in a table in one of our reviews as having qualified as being picked on the basis of a QTc greater than 500 milliseconds or a change that was longer than 80 milliseconds.

There were 3 subjects that had no U-wave at baseline. There were -- I can't count the number of bars -- this number of subjects that had no baseline U but had a U on therapy, this that had a U at baseline but no U on therapy, and this number of patients that had U's both at baseline and on therapy.

Where there were U's present, the QT was estimated as best as you could and obviously with great error, but if you pay attention to the gray versus green and pink versus yellow, what you see is there was no interval change.

I point out that the doses here are anything from 50 to 200. So, these changes, although they are most readily noticeable at high doses, do not depend on high doses being present. This is a continuous relationship. It just is more easy to see as the dose increases.

This is a group of patients in the hypertension study that were in the 200 milligram arm, and you see it's the same pattern. Sometimes there were U's, sometimes there weren't U's, and so on and so forth, but where you

just look across the bars, if anything there was a decrease in interval.

So, if the statement that no increase in interval occurs, I concur. That something happens between the S-wave and the P-wave as a function of the dose of mibefradil, however, is also equally clear.

Now, my credibility is probably in question because I called this a U. How could you see so many U's? People don't have U's. Right? So, this is a patient and I called this a U and this a U at baseline in a precordial lead. Keep that image in mind and forget it for the moment.

If you look at that same patient at baseline and at week 4 in a limb lead, there isn't any question that the QT got longer. But if you look in the limb lead, here's that U I called, and clearly the longer QT is a function of there being a U present. So, where you look on the cardiogram makes you draw a different conclusion, and if this is not a long QT because there is a U, you know that because you see it somewhere else.

And this is another U at baseline, and it's the same phenomenon. If you look in the limb lead, I've never seen a long QT if that isn't a long QT, but in the precordial lead, you clearly see the U growing and the T

getting smaller and then finally ending up with a very long QT.

And the same in another one so that once again looking in the limb leads, that is a long QT, but if you look in the precordial leads, you see that there's something going on.

So, in summary, I'm comfortable making the declaration that there are no changes in intervals. I want to leave that, though, with the question of whether one knows that it is the intervals that matter and not whether what is happening during the SP is important.

DR. KOBRIN: Now that we have seen what is happening with the supratherapeutic doses, let me show you what is happening with the recommended doses of mibefradil.

We looked at the change from baseline in QTc interval at each study of the placebo-controlled studies. We can see here placebo in blue, 50 milligrams mibefradil in green, across the studies, and in each study the change from baseline in QTc interval was either similar to placebo or there was a larger decrease in QTc interval. And the overall effect from all these studies, no change in the placebo group and a decrease in mibefradil group with the 50 milligram dose, a decrease in the mean change from baseline in QTc interval.

With the 100 milligram dose, we have seen the same thing by study. In the placebo-controlled studies, each dose versus its relevant placebo, we can see across the studies and the overall effect. In the placebo, no change as expected. In the treatment group, a decrease in mean change from baseline in QTc interval.

We looked at high risk populations, patients on chronic diuretic treatment, elderly patients, patients with ischemic heart disease, patients with congestive heart failure, patients with congestive heart failure on chronic furosemide treatment, with the recommended doses, and we can see the same picture: a decrease compared to placebo in blue in each study with the 50 and 100 milligram doses when it comes to the QTc interval.

We wanted to see what is the relationship between baseline QTc and the change from baseline in QTc. We can see it in the next slide. We see if the patient had baseline QTc between 400 to 450, 450 to 500, 500 to 600, and we can see if we go across the doses, the recommended doses, and even the supratherapeutic doses, the higher the baseline QTc, the larger the decrease in mean change from baseline in QTc and the overall effect.

We see that we had about 430 patients with a relatively long QTc at baseline. We did not exclude any

patients with long QTc because we were not aware of any problem with this issue.

The next step that we did -- and we know, by the way, that with drugs that adversely affect QTc, there is a very clear dose-related increase in QTc interval. We don't see it with mibefradil.

We looked at concentration effect. We see here the results in the three hypertension studies. We see the concentrations and the change from baseline in QTc. The blue line is the 0 line, and the red line is the smooth observation line. We can see that it goes along the 0 line.

If we look at high risk populations, congestive heart failure patients with the recommended doses, you can see the 0 line and the smooth observation line. Definitely when we go to high concentrations, you don't see a concentration of points at the high levels. Even if we look at patients with congestive heart failure on furosemide treatment, in fact there is a tendency to decrease.

When you have a drug that adversely affects the QTc, this is what you see. This is sotalol. You don't see it with mibefradil with this aspect.

The next thing that we did, we had an

electrophysiology study that we did early in our program mainly to look at the AV node, but we looked of course, now that we had this issue, at other parameters.

Now, in this study we wanted to reach by infusion concentration levels that are at peak or at least at trough based on what we know that are the concentrations of the drug in the plasma. This is after chronic administration of 50 milligram or 100 milligram. What we reached are these concentrations which are above the trough levels but below the peak levels.

This was a large study relatively. 71 patients were randomized to receive either placebo, the dose 1 which is the 50 milligram, and dose 2 which is the 100 milligram. We see the reasons for electrophysiology. Most of them were because of rhythm disorder or post-radiofrequency ablation. The baseline characteristics were the same in the three groups.

The parameters that we looked at were sinus node function, the AV node function, and also below the AV node function. The only significant changes that we have seen were as expected.

We had a slight increase in the corrected sinus node recovery time with the 100 milligram dose that almost reached statistical level, .053. There was a significant

increase of AH interval at the 100 milligram dose, and the Wenckebach point with the 50 and 100. There was no change in the effective refractory period of the atrium. There was no change in the ventricular effective refractory period, and there was no change in HV. As we have seen from Dr. Ruskin, drugs that adversely affect the action potential, there is an increase in the refractory period of the atrium, the ventricle, and the HV.

What we see here is what one would expect to see with drugs like verapamil and diltiazem. It's not different, and it's consistent with the fact that the drug does not prolong action potential. In fact, it lowers the action potential, and this is why we see only the effects on the sinus node and the AV node.

From this point I would like to move to the safety of this drug.

Yes?

DR. MOYE: Just one question. I appreciate the importance of the information you provided about relationships between changes in QTc and in different high risk populations. But given the revelation that we have between Dr. Lipicky and yourself that what's going on is not perhaps QT but something else like U-waves, isn't it also important to look at something like the incidence of

new U-waves with therapy?

DR. KOBRIN: Yes, I agree. We looked at the incidence of these T-U morphological changes, what is happening. In order to do this, we collected the ECGs from the upper quartile of QTc at end of treatment, which is a relatively conservative way, to see what is the incidence of these changes.

We found that the incidence was 1 percent at the 50 milligram dose, 4 percent at the 100 milligram dose, 12 percent at the 150 milligram dose, and 30 percent at the 200 milligram dose. So, it was clearly dose-related, rarely seen at the recommended doses, higher at the higher doses. This is why these morphological changes affected the QT in such a way that we had an apparent increase in QTc.

In order to see if there is any clinical relevance to these U-waves, I think that the most important thing is to look at events of the safety database, and this is why we looked at these events which represent arrhythmic and potentially arrhythmic events.

DR. MOYE: Just one brief question. Excuse me.

DR. KOBRIN: Yes.

DR. MOYE: Why did you look at the upper quartile of QTc?

DR. KOBRIN: We were unable to collect everything, so in order to be on the conservative side -- and we know that these morphological changes cause an apparent increase in QTc -- we said we will collect all the upper quartile because if there are morphological changes, this is where we will find them. Therefore, the incidences that we have seen, I think it's conservative. If you would look at the whole database, we might see lower incidences.

So, looking at the safety, we concentrated on this event. This is because we know that it's so difficult to see torsades, to see ventricular arrhythmias, and the only way sometimes to identify it is by looking at these events.

Looking first at syncope in the controlled studies, in the hypertension placebo-controlled, angina placebo-controlled, both indications placebo-controlled, and in the comparative studies, what we can clearly see, that in the hypertension the incidence of syncope was higher on placebo than on mibefradil. Similar in angina. Overall in both indications, more on placebo. In the comparative studies, similar incidence. Definitely we don't see an increased incidence of syncope which might be a signal that something is going on.

Looking at high risk populations for syncope,

women and elderly, what we have seen -- and here in the middle is mibefradil on the angina hypertension database, and we see that in women the incidence was lower than men for syncope, and in elderly lower than in non-elderly. On placebo and on comparator, we have seen what one would expect, a slightly higher incidence. We haven't see it here in mibefradil in these high risk populations.

Ventricular tachycardia events we have seen in five cases: 1 out of 183 on amlodipine, 1 out of 295 on placebo, and 3 out of 3,430 patients on mibefradil. Let me tell you a few details about these three cases.

One case was an asymptomatic event observed on telemetry after stopping atenolol. This is in the 446 study, and this was a preplanned hospitalization.

One patient was diagnosed as having primary prolonged QT syndrome. He was hospitalized because of syncope, and 5 days after stopping all treatment on programmed stimulation, they were able to induce non-sustained VT. It was decided to implant a defibrillator in this patient and since the defibrillator was implanted, it went off 11 times.

The third patient was the only patient where we have seen torsades. This was a patient with a history of long QT, a family history of sudden death at young age,

mother and grandmother. This patient during the study was put on cisapride treatment, and we know that cisapride can prolong QT and cause torsades and mibefradil itself can interfere with the metabolism of cisapride and cause an increase in cisapride concentration. We think that this event occurred because of cisapride.

So, if we look at the syncope events and the VT events overall in the controlled studies, we can see that there was definitely no signal there was increase in syncope or increase in VT among the patients treated with mibefradil.

What about death? Sudden death we have seen in the angina/hypertension program one case. If we look specifically into this case on this slide, what we can see, this was a 70-year-old black male treated with mibefradil 50 milligram, and the event occurred on the day 302 of treatment. Potassium level during the treatment did not change. The patient was on potassium chloride during treatment. We can see here the QTc during the treatment which did not change, and there were no events during this study in this patient.

Overall when we look at the death rate on the mibefradil program, we have seen the following.

In the placebo-controlled studies, there was

one death. It occurred in an elderly woman, 92-year-old, in an elderly home because of mesenteric thrombosis, and she was treated with 12.5 milligram of mibefradil which is a noneffective dose.

There was one death on the comparator and one death on mibefradil in the active-controlled studies.

So, overall in the controlled studies 1 out of 1,000 on placebo or comparator and 2 out of 2,000 on mibefradil.

In the long-term safety studies, there were no deaths in the hypertension. There were four deaths in the angina. One of them was the sudden death that I've told you before after 300 days of treatment. And these deaths were not unexpected in this patient population, and overall this was the event rate for both indications in the open-label studies.

Mibefradil, as you heard, is being developed for the treatment of congestive heart failure. This is being done in the MACH 1 study which is a mortality assessment in patients with congestive heart failure. This is an event-driven study that will be stopped after 369 deaths.

The pilot study was finished when this study was running. The pilot study was designed to look at signs

and symptoms of congestive heart failure. When this study was finished, what we have seen, that there were 6 deaths on the mibefradil-treated patients. We looked at each case specifically to see if there were any specific events, change in QTc, morphological changes, potassium changes. We couldn't find any link between the deaths and mibefradil.

However, we informed the Safety Committee of MACH 1 about this finding. We informed the Safety Committee of MACH 1 about the T-U morphological changes, telling them that the FDA raised a safety concern regarding arrhythmic potential of the drug, and they were asked to look into this specific issue when they did their third interim analysis, and the results of it were recently communicated to the sponsor.

At this stage, 2,400 patients were randomized in the study; the mean follow-up, 304 days; 268 deaths, among these, 142 sudden deaths based on Physical Event Committee evaluation. The Safety Committee, after being told about the pilot study, about the T-U morphological changes, and the concern of the FDA, informed us that the study should continue.

In addition, we have 4,700 patients since our clinical cutoff, 50 percent on mibefradil. On this

database, we have five deaths. Only one of them was an unwitnessed death in nursing home 13 days after abdominal surgery for liver mass.

So, in fact, ladies and gentlemen, we have looked at the angina/hypertension database, which is about 3,500 patients, the MACH 1 database, which is 2,400 patients, half of which on mibefradil 100 milligram. We have the phase IIIb database, which again 4,700 patients, half of the patients on mibefradil. And there is no signal that there is arrhythmic or potentially arrhythmic risk with the drug.

In summary, treatment with mibefradil or the presence of mibefradil is associated with a decrease in the myocardial action potential, and this is very important in our mind because drugs that adversely affect repolarization, prolong action potential.

At the recommended doses, the QTc interval is decreased, including in high risk populations.

There is a dose-related increased incidence of T-U morphological changes. As a result of these morphological changes, we have this apparent increase at the 200 milligram dose, which is twice recommended doses of the drug.

Similar morphological changes were seen with

verapamil and diltiazem, and again, as was mentioned by Dr. Tomaselli, these morphological changes are consistent with the decrease in the action potential. If you will be interested later on, we will be able to show you why it is consistent with a decrease in the action potential.

In the preclinical studies, looking at all the models of torsades, no evidence of proarrhythmic effect.

And in the clinical databases that we have seen, no evidence for arrhythmic or potentially arrhythmic events, including high risk populations.

In conclusion, mibefradil is an effective antihypertensive, antianginal, and anti-ischemic compound. At its recommended doses, it is very well tolerated. Treatment with mibefradil is not associated with an increase in QTc, and there is no evidence that the observed changes in T-U morphology observed with mibefradil -- and as we have seen with verapamil and diltiazem -- is clinically relevant.

With this, we conclude our presentation, and we'll be ready to answer your questions.

DR. MASSIE: Thank you very much.

Why don't we finish up our discussion here on your recommendations before we take a break?

Ray?

DR. LIPICKY: Can I ask a couple of questions? When mibefradil is given, what is its volume of distribution?

DR. KOBRIN: 200 liters.

DR. LIPICKY: 200 liters. So, it's not limited to the extracellular space.

DR. KOBRIN: That is correct.

DR. LIPICKY: Do you know what the concentrations of mibefradil or its metabolites are intracellularly?

DR. KOBRIN: Do you know? No.

DR. LIPICKY: No. Good. I didn't think you did.

(Laughter.)

DR. LIPICKY: The in vitro electrophysiology studies were all intact cells? Yes, that is correct.

So, they were short-term, short duration. They were less than a day.

DR. ERTEL: They were less than a day.

DR. LIPICKY: Okay.

DR. MASSIE: Can you please use the microphone, both of you?

DR. LIPICKY: I'm sorry.

DR. ERTEL: I'm Eric Ertel, Cellular

Electrophysiologist.

DR. LIPICKY: So, it was less than a day.

Clearly what you were studying were the effects of the drug when it was exposed to the external surface of the membrane.

DR. ERTEL: That is correct essentially, yes.

DR. LIPICKY: And is there reason to believe that drug effects may not be the same when they are given outside to the external surface of the membrane versus inside to the internal surface of the membrane?

DR. ERTEL: There is no specific reason to believe so, no.

DR. LIPICKY: Well, how about TEA?

DR. ERTEL: Mibefradil specifically --

DR. LIPICKY: Well, but the reason --

DR. ERTEL: There are plenty of examples of drugs which --

DR. LIPICKY: There are many examples of drugs that when externally applied do not behave the same qualitatively as when internally applied.

DR. ERTEL: That's right.

DR. LIPICKY: So, although the data that you show is very interesting, it has a hole in it.

DR. CLOZEL: I think that when you give very

high doses of a drug and you wait a certain time -- it's true for every drug -- there is going to have a certain -- because the drug is lipophylic, it is going to have a certain penetration. It's going to work. If you give order of magnitude -- and this is why we went two doses, very high, not to miss an effect.

So, I think that for the in vitro experiments, I think by giving very high doses, we can compensate for any change that a little part of the drug would penetrate.

DR. LIPICKY: All right.

Then I guess the second question is that there is no question in your mind that this has the ability to block IKr.

DR. KOBRIN: Maybe Dr. Tomaselli would like to answer this.

DR. TOMASELLI: There is no question that this drug has the ability to block IKr, as does verapamil, as does --

DR. LIPICKY: No, no. That's okay. I understand.

(Laughter.)

DR. TOMASELLI: Can I make one other comment about IKr block?

First, the system that was studied was either

mouse tumor cells or the channel expressed in frog eggs. You need to be very careful about extrapolating that data to the native channel in the native cell. I think the bottom line is that regardless of the concentration or the duration of exposure, there is no prolongation of action potential duration emblematic of IKr block.

DR. LIPICKY: Right, okay. How do you explain that? That mystifies me. Since clearly blockade of IKr can affect the duration of an action potential and you have a compound that has the ability to block IKr and you went over three orders of magnitude concentration change, how do you account for the observation?

DR. KOBRIN: Dr. Sanguinetti maybe can answer this.

DR. SANGUINETTI: It's also blocking calcium current at these concentrations. In fact, due to the voltage-dependent block of calcium current, the IC50 is actually much lower for calcium current than it is for IKr, and that's the most important point here.

DR. KOBRIN: The most important thing in fact is the fact that it lowers the action potential, the bottom line.

DR. SANGUINETTI: Well, yes. I'm talking about in terms of comparing IKr and L-type calcium channel block.

But the most important thing is certainly that it shortens action potential, never prolongs.

DR. LIPICKY: So, what you're saying is the IC50 for calcium channel block is much lower than that for IKr block.

DR. SANGUINETTI: Yes, if you consider the voltage dependence of block of L-type calcium channels, that's correct.

DR. LIPICKY: But shouldn't at some point things reverse? I mean, sooner or later you're going to have all of the calcium blocked, and then you're going to start seeing the IKr influence. It ought to get longer somewhere.

DR. SANGUINETTI: Right, and in fact that experiment was done on action potentials where I think --

DR. LIPICKY: Well, but all you've shown us is that it shortens.

DR. SANGUINETTI: No, but in the presence of --

DR. LIPICKY: It's biphasic. It has some -- you know, it shortens and then it lengthens?

DR. SANGUINETTI: No, it doesn't do that.

In the presence of nisoldipine, which shortens action potential considerably to 30 percent or so of normal, if you then add mibefradil, there's no increase.

And we've done that exact, same experiment with dofetelide. We see a dramatic increase in action potential duration and the same amount of nisoldipine pretreatment.

To me that's very good evidence that if IKr block is occurring, which I think it is, it's not very important. It doesn't overcome the more important effect that you've shortened the action potential due to calcium channel block.

DR. CLOZEL: I think that we have to mention that in native cardiac cells, not in tumor cells or not in recombinant preparation, we have seen, if anything, a very weak block of IKr. It is small even at 10 micromolar. So, I think that all the experiments that we have done just show that maybe we cannot exclude a block of IKr, but certainly in cardiac myocytes this is very small, very limited and overwhelmed clearly by calcium channel blockade.

DR. LIPICKY: Okay, I'm not sure I understand that, but that's all right. I don't know what to ask to pursue it.

Then the very last question I have is, what incidence of mibefradil-induced sudden death would be acceptable in an antihypertensive patient population to you?

DR. KOBRIN: I think that it's unacceptable.

DR. LIPICKY: No. What exact incidence? 1 in 1,000, 1 in 10,000, 1 in 100,000?

DR. KOBRIN: Depending what is the cause of the sudden death, I think that if it's drug-induced, we wouldn't accept it. I don't think that mibefradil is associated with this.

DR. LIPICKY: Well, what incidence do you think you have excluded with what is -- I admit --

DR. KOBRIN: I don't think we can --

DR. LIPICKY: -- it's a very large clinical trial database. I'm not taking away from that, but what incidence do you think you have excluded?

DR. KOBRIN: I think that in this NDA, as in any other NDA, we cannot exclude incidence of less than 1 in 1,000. As in any NDA, I think that's the situation. If we look at 3,500 patients here, but also if we look at what is going on in the MACH 1 and the phase IIIb where we don't see a signal on this respect, I think it's very comforting that we don't have a problem with this issue. Again, as you said, we cannot exclude unless we will expose the drug to 100,000 patients.

DR. MASSIE: You've brought up the MACH 1 trial on which I actually am an investigator. The Data and

Safety Monitoring Committee obviously has its main marching orders to protect the patients in that trial and to protect the integrity of the trial. It sounds like their statement was a fairly nonspecific one.

Maybe you can tell us a little bit about the stopping rules --

DR. KOBRIN: Maybe Dr. Neumann, our statistician, could show you this point?

DR. MASSIE: And a little bit more about if they did any qualification other than that simple statement. In other words, do we have an idea -- given the information you provided them about a risk of sudden death and the increased death in the heart failure trial, any information about whether they would have altered their stopping rules, what types of things might have stimulated them to take an --

DR. KOBRIN: As you know, this is an independent committee. We don't have any influence on what they do. What we do know, that they looked specifically into the issue of arrhythmic and potentially arrhythmic deaths when they did their evaluation of their interim analysis. What exactly they did, I don't know. The only thing that I know, that they told us, knowing again the pilot study, knowing the concern of the FDA, that the study

should continue.

Dr. Norbert Neumann will show you what are the assumptions that we can put regarding this point.

DR. MASSIE: I think that would be worth doing.

DR. NEUMANN: Norbert Neumann, statistics.

Please, can I have carrousel number 41, slide number 22?

In MACH 1, the interim analysis follow stopping rules according to O'Brien-Fleming. In our analysis of what is the interpretation of the statement that the trial can continue, I distinguish between stopping for efficacy and giving a warning light for safety. The stop for efficacy would be reviewed in case we have 107 deaths in the mibefradil compared to 161 in the mibefradil group which, according to a risk reduction of about one-third compared to placebo. Definitely with 268 deaths, we have complete neutrality in the case of 134 against 134.

I assumed a warning limit, which is actually specified in the protocol, of 10 percent in a statistical test. This definitely should not cause the stopping of the trial, but should cause an action of the Safety Board by asking for further data, further analysis, and so on. This is assuming I came to a limit of 147 deaths which would cause a warning light of the Safety Board.

We received the information we can continue with the trial. We do as planned in the protocol our fourth interim analysis, and from this point of view, I strongly assume that they are between the limits of 107 to 147 death cases in the mibefradil group compared to 161 to 121 in the placebo group.

DR. MASSIE: Is it possible they could have reached that warning limit and you wouldn't be aware of it?

DR. NEUMANN: I'm sorry?

DR. MASSIE: Is it possible they could have reached that warning limit, but because they did not require additional information, you might not be aware of it?

DR. NEUMANN: It is possible. I agree this is an assumption, but as I said, the limit of 10 percent in the p value of the analysis is written in the protocol as a safety warning, and we got no signal that we have reached this limit.

In particular, we have alerted the Safety Board on the issues we just raised on the results of the pilot CHF trials and also on the issue with the QTc changes. Therefore, I conclude that we are within the limits given in the --

DR. DiMARCO: I think Dr. Massie's question is

suppose they decided to ignore the warning. What was the stop limit?

DR. NEUMANN: The formal stopping rule in the protocol is two-sided and would be the same stopping rule as for efficacy in the upper limit just in the other direction with 161 in the mibefradil group and 107 in the placebo group.

DR. CALIFF: Do you have the composition of the committee or who the people are who are on it?

DR. NEUMANN: Sorry?

DR. MASSIE: He wants to know the members of the Data and Safety Monitoring Committee.

DR. LINDBERG: Elisabet Lindberg, clinical research.

Dick Conti is the chairman of the committee. The rest of the members consist of Bertram Pitt, Phil Wilson, and Professor Hugenholtz, and there's an independent statistician from the University of Freiburg, Manfred Olschewski.

DR. MASSIE: Maybe we can go to John now.

DR. DiMARCO: Yes. I have a number of questions.

For Dr. Tomaselli, in the torsades models was mibefradil studied at several concentrations, the highest

tolerated concentration, single concentration?

DR. TOMASELLI: I think it differed depending upon the model, and Dr. Clozel, who actually performed some of the studies, can address the specifics of the protocols. I would also hasten to add that these were all standard protocols described by other investigators and the protocols were followed as they are published in the literature.

DR. CLOZEL: I think it's a very important question, the question of the dose, because of course we didn't want to miss any effect. I think that in order not to miss any effect in this type of model, it's very important to choose a dose range. Except for the cesium model, for the two other models, we chose a dose range starting from the minimum hemodynamic effect up to the toxic dose, a dose which produced complete AV block and where we cannot go further because it was not possible.

DR. DiMARCO: So, the data that you presented where the numbers were 0 was across all dose concentrations.

MR. LUCEK: Absolutely.

DR. DiMARCO: Did you look at interactions with drugs? In other words, did you look at, say, a dose of sotalol or a concentration of sotalol that did not produce

torsades in one of those models and add mibefradil?

DR. CLOZEL: We did not look specifically at sotalol experiment --

DR. DiMARCO: Or any of the drugs.

DR. CLOZEL: Yes, but in fact the cesium model -- cesium is a blocker of potassium, and it's a fact it's the same thing as giving sotalol. Since it has been well described, this is why we used cesium, and cesium per se is like sotalol reproduced torsades de pointes. The type of experiments we did with cesium is to give cesium dose ascending and to give with and without the drug.

So, it's exactly as you asked. As you have seen, it decreases like other calcium antagonists. It decreases the incidence of torsades de pointes induced by cesium.

DR. DiMARCO: In the whole animal models, did you try infusions of either potassium or calcium or magnesium to see if they would change the electrocardiographic phenomenon?

DR. CLOZEL: No, we did not, and the reason is rather simple. It's technically. You have seen that in order not to miss such effects on the electrocardiogram, you have to have the animals in a slow heart rate because, as you know, even in man the U-wave or whatever will

disappear at high heart rate. In order not to have a high heart rate, you must not be next to the animal. You must not induce stress, and infusion of this drug would require perfusion and will require to have all the complication of anesthesia or stress which would disappear which in this condition we would not be able to see morphological changes.

This is why what you have seen here, what Dr. Tomaselli has shown is experiments performed with specifically telemetry system in order to have the best conditions to study these changes.

DR. DiMARCO: Just a couple of questions for Dr. Kobrin.

In your database, a lot of the patients -- I think the percentage of women is somewhat lower. It's about a 2 to 1 ratio, male to female, in the whole database, and in the angina database, it's about 5 to 1. In MACH 1, have you tried to recruit a reasonable number of women, since obviously they seem to have a higher incidence of torsades and polymorphic VT?

DR. KOBRIN: Dr. Lindberg, do you know? We don't have an answer to this.

In the hypertension, by the way, the ratio was 1 to 1 and in angina it was 5 to 1. As always is happening

in angina studies, there are more men going into these studies than women.

DR. DiMARCO: Do you actually have the EKGs on either the patient with the familial long QT syndrome or the cisapride patients for us to look at to review?

DR. KOBRIN: I don't have the ECGs. I have the QTc interval, if you would like to see.

DR. DiMARCO: You know, we're talking about morphologic changes and we've been talking about measurements, but do you actually --

DR. KOBRIN: I don't have the ECGs, but I can tell you that the patient who had the prolonged QT, it was a typical congenital prolonged QT pattern on the baseline ECG and after stopping the trial and we can see the typical changes that we see in congenital prolonged QT syndrome in this case.

DR. DiMARCO: Which typical pattern?

DR. MASSIE: Would it be possible, do you think, to have this faxed to you?

DR. KOBRIN: Excuse me?

DR. MASSIE: How difficult would it be to get these ECGs faxed here in the next hour and a half or so?

DR. KOBRIN: I can get the ECGs during the break, if you want.

DR. MASSIE: Okay. Maybe you could ask for those.

DR. KOBRIN: I have them with me. I just need to find them.

DR. DiMARCO: Okay.

Do you know -- I must have missed this in the database -- what percentage in either your hypertension or your angina trials had left ventricular hypertrophy?

DR. KOBRIN: We didn't do specifically echocardiograms to look into this point. We have recently, however, finished a specific study in patients with left ventricular hypertrophy where we compared mibefradil to atenolol on the regression of left ventricular hypertrophy. This was a 6-month study where we looked into these issues. There was a significant decrease in left ventricular hypertrophy with mibefradil, and there were no problems in this.

DR. DiMARCO: This is a question for Dr. Ruskin. If we accept the position that these morphologic changes are of little clinical significance, what would you do if you saw them during therapy in a patient?

DR. RUSKIN: Well, I've thought a lot about that. I think if I saw the T-wave notching or the T-wave flattening with most of these changes, I would do nothing

based on what I know about the drug and what it does electrophysiologically.

In all honesty, if I saw gargantuan U-waves and a really frightening looking appearing EKG, I would probably reduce the dose or change the drug, given the fact that I have other options. That would be acting from my gut and not from scientific data. I don't think I would chase those things or go looking for them, but if you presented that EKG to me, I would act as I've suggested.

DR. KOBRIN: Dr. Pratt would like to add to this.

DR. PRATT: Just to elaborate on that a little bit. This is Craig Pratt.

We actually were concerned enough about the ECG changes that we saw at high doses of mibefradil, diltiazem, and verapamil that, in cooperation with Dr. Fenichel, we sent 15 ECGs blinded to treatment assignment to three electrophysiologists asking them if they would be concerned. Now, I didn't ask them your second question, what would they do, but the level of concern was equal between the changes we see with those three agents that otherwise have a similar electrophysiologic profile.

DR. RUSKIN: John, I guess I would just have to add that if I saw an EKG on verapamil or diltiazem that

looked like that, I would do the same thing.

DR. DiMARCO: In terms of if we again accept that these are of no significance, can you sort of postulate what you think the requirements or what the restrictions on the use of drugs known to prolong the QT interval? Do you have any data about interactions of changes like this with other drugs like quinidine, amiodarone, any of the arrhythmic drugs? Because we know if it's released in the general population, there will be people on those medications.

DR. KOBRIN: Let me answer this question. We don't know specifically what it does. We looked at the literature to see what exactly is going on with this kind of drug. What we have seen is the following.

We have seen clearly that with this drug there is prolongation of the QTc. There could be sometimes morphological changes, and there is a shift of the peak of the T-wave to the right, something that you don't see with mibefradil. Again, at the recommended doses, mibefradil shortens the QTc interval and you can measure it correctly. With the other drugs without morphological changes there is a prolongation of the QTc.

DR. DiMARCO: My last question I guess right now is, when you presented the QTc data, is that hand-

overread QTc data or is that machine-read QTc data? I just couldn't follow at what point in time, when you presented data, you made those measurements.

DR. KOBRIN: Whenever I showed you the mean changes from baseline, this was based on, in most cases, an ECG reading or on investigator reading on the blinded fashion on a prospective fashion during the study -- in the duration of the study. So, all these data are based on either ECG or investigator evaluation based on what they read. Sometimes they were overreading the ECGs and sometimes they did not.

DR. DiMARCO: So, you didn't control the investigators. I realize how difficult it would have been, but these are just what came out of the machine or the way the investigator read them.

DR. KOBRIN: Either machine or investigators, yes.

DR. DiMARCO: My last comment. I'd like to congratulate Dr. Lipicky that he actually got through 38 ECGs looking at all the QT intervals. That's about 36 more than I can ever get through.

(Laughter.)

DR. MASSIE: Ray, why don't you go next, and then Dr. Weber.

DR. LIPICKY: I wanted to ask Dr. DiMarco whether he thinks that those animal models have good predictive value because you were pursuing it. We happen to know of one circumstance where there was an investigational drug worked up that went through those same animal models, came out clean, and in the first three people it went into, it caused torsades. Is that an unusual thing or we just a victim of chance or what?

DR. DiMARCO: I think that's unusual, but those models have been used to study drugs that are usually IKr blockers by particular mechanisms. So, they're sort of standard models, but they're not the only times that polymorphic ventricular tachycardia occur.

DR. LIPICKY: Should we ignore our experience with that one drug as being way out?

DR. DiMARCO: Well, I think the experience there was that three individuals, patients, developed that problem. Here you have a much larger database of patients in which you haven't seen that yet.

DR. TOMASELLI: May I make a comment about that? Can you put carrousel 34, slide 23 up for me please?

I believe that this represents the drug X in question. One of the things that one has to be very careful about is that if you look at the entire profile, as

has been looked at with mibefradil, there are several striking changes between this drug and this drug.

First and most importantly, at all concentrations mibefradil shortens action potential duration. This drug does too at high concentration, but at lower concentration this drug prolongs action potential duration.

In addition, there is an almost two order of magnitude difference in the sensitivity of IKr to this channel compared to this channel. So, despite the fact that there may be some even electrocardiographic superficial similarities between the drugs, the electrophysiologic profiles are very, very different.

DR. CLOZEL: I'm sorry. Can I just make one more comment?

It is very important, when we look at this preclinical program, to look at the global program. So, the first thing you have seen in action potential, there is no one exception, no one drug, which gives torsades de pointes in man and which does not prolong action potential. So, there is no one exception first of all. So, if you see a drug which prolongs action potential, it is maybe at least the best candidate. It's not sure but it is a very good candidate.

Then you go further. You got to your model of torsades de pointes. If you go the first model, it doesn't work. Maybe drug X has been tested in one model and it doesn't work. It is not sufficient. This is why you have to go to several models, and you have to look at this whole program to really assess the potential proarrhythmic effect of the drug.

So, really just by looking at the effect of drug X on action potential, I would have been very concerned from the very beginning.

DR. DiMARCO: Let's move on. Mike is our second reviewer, and then we'll move through the committee.

DR. WEBER: Well, there are not too many things that I'm certain of, but one of them is that I am not an electrophysiologist.

So, the one question I have I want to give to Dr. Ruskin and Dr. Pratt is to get back to what seems to be the main issue and the main finding, that we're looking at a morphologic phenomenon, the appearance of U-waves. This is probably the first time that any group of people have sat down to really think about the importance of this phenomenon. As Ray and others have pointed out, often they are baseline. Sometimes they get bigger during treatment, sometimes smaller, sometimes they get big and then smaller.

While we're sort of struggling to know if this has any meaning, we've taken comfort -- and I assume we're meant to take comfort from the fact that a similar phenomenon is seen with diltiazem and verapamil.

What I'd really like to know is it, first of all, morphologically the same phenomenon with those other calcium channel blockers.

Secondly, do you have any sense of the incidence with those other calcium channel blockers of the changes in U-waves?

And perhaps most importantly, do we have any sense that there might be some hidden clinical problems with those other calcium channel blockers? We all assume that verapamil and diltiazem are safe drugs. They've been used widely for many years and with a great deal of confidence by all of us. Have we been missing something?

So, the morphology, the incidence, and the possible clinical implications.

DR. RUSKIN: I have to take the second question first. I have no idea what the incidence is. I will make a personal comment about that, though.

I think that qualitatively, from looking at the EKGs, the changes are similar among the three drugs. What was so striking to me, when I first saw these, was that I

didn't believe they could be explained on that basis because they were the kinds of EKG changes that I have been taught to respond to with great fear, and when I looked at the EKGs, I was astounded. If you had told me that similar changes could be seen with commonly used calcium blockers, I would have said that's impossible. It doesn't happen. I've never seen it.

I think it does happen. I think it's more common at high doses, and I think that certainly I have not made a careful study of the EKGs even at standard doses of verapamil and diltiazem. I'm reasonably confident that the really striking changes seen with high-dose mibefradil and high-dose diltiazem and verapamil are not common at therapeutic doses, but I don't know what the incidence is.

With regard to the question of the potential malignancy of these findings, I have no firm database, scientific answer. What we do have or what I have take away from this material is that the basic electrophysiology and the clinical electrophysiology are not compatible with any drug or class of drugs that have been shown to cause torsades.

If the question is, could there be some previously unknown, undefined mechanism by which these changes may have some adverse effect, I think the answer to

that is we don't know. I think we don't have that information.

My overall level of comfort, though, based on the combination of a very, very extensive preclinical database and clinical observations, is very high.

DR. MASSIE: Let me just toss in one other question related to morphology there. Bepridil. How does the morphology of these changes compare to bepridil?

DR. RUSKIN: Well, bepridil is well known to have striking effects on action potential duration and on the QT interval.

DR. MASSIE: I understand that, but just in terms of the precise morphology.

DR. RUSKIN: I don't have an answer to that. I've used bepridil in the past at very small doses and in very small numbers of patients, but I have not been aware of comparable kinds of EKG changes.

DR. LIPICKY: The same question I guess that Barry is asking. Do you know that there has been some systematic look at terfenadine or sotalol or quinidine and that similar kinds of things have not been see there?

I must admit I never read a U-wave before in my whole life. Now everyone has them.

(Laughter.)

DR. RUSKIN: It's a new discovery.

DR. WEBER: Actually we're starting to call them Lipicky waves in honor of --

(Laughter.)

DR. DiMARCO: I can comment on that. I don't think there's anything, other than there's a lot of abnormality -- I saw ST segment elevation. I saw T-wave flattening. I saw ST segment almost depression. The U-waves did get better. Then some of them were humps. Some of them were just isolations off the baseline. I think I've seen that with other antiarrhythmic drugs and other drugs.

When I made the comment about a typical QT interval in people with long-term QT syndrome, there's a lot of variability in those people as well. There's nothing here I think that you can actually pinpoint as this is only seen with this drug. I think this is why we're having a problem because similar phenomena are seen with drugs that we know cause torsades.

DR. MASSIE: Bob?

DR. TEMPLE: I don't think that's the crucial question.

The electrocardiograms that the consultant -- Dr. Lipicky read were identified by individuals and by

machines as showing prolonged QT, the very sort of thing that makes us all get frightened. Along with animal data, the theory here is that they weren't what they seemed to be. They were actually morphologic changes. Therefore, we shouldn't be worried.

But there's a crucial logical connection, which is that if you were to look at the drugs you are worried about, terfenadine, astemizole, and things like that, Dr. Lipicky would not be able to resolve them into morphologic changes. They would continue to look like actual QT prolongation.

The question is, is there a database one can look at to get some feeling that that's true, or do people actually know that from their experience?

It's important to remember, we sent those electrocardiograms out to three reasonably sophisticated, advisory committee trained cardiologists, and they all thought they were QT prolongations. So, it's only now in retrospect with further analysis, looking at the chest leads, and all that kind of stuff, that perhaps some insight to that has been turned up.

The question is, if you did that with terfenadine, would you find the same thing or not? How can one answer that?

DR. KOBRIN: Let me just add one more point to what was said. Electrocardiograms for mibefradil, verapamil, and diltiazem were also sent to three prominent cardiologists. One of them was the same cardiologists on both and they said that verapamil, diltiazem, and mibefradil electrocardiograms looked the same for them. So, the same reaction was for them.

Now, regarding the question that was asked here --

DR. TEMPLE: Before you leave that, you take more assurance from that, I must say, than I do. Those are very high doses of verapamil and diltiazem, not commonly used. If they had a problem at those doses, we would hardly know it because those are not doses that are used.

The more pertinent question is, for the drugs that are a problem, sotalol and things like that, could you, could Ray resolve all those into U-wave and T-wave morphologic changes too or not?

DR. KOBRIN: The only thing that I can add to this is the following. Looking at the literature -- because we wanted to see this in the literature -- it's very difficult to find what was the method that was used to measure the ECGs. However, in many publications the method that was used was the Lapeshkin method which is the QT is

up to the kink between the T and the U and it doesn't matter if you find it only in one lead or in one complex.

If you follow this methodology, drugs like bepridil, sotalol, and I think quinidine -- I'm not sure about quinidine, but at least bepridil and sotalol, there was a very clear prolongation of the QT going through this method. If you go through this method -- this is what we did with Dr. Lipicky -- there is no prolongation of QT with mibefradil.

DR. DiMARCO: What about dispersion?

DR. KOBRIN: And Dr. Pratt would like to answer also.

DR. PRATT: This is for Bob Temple. The trial that I did in cooperation with Dr. Fenichel included a verapamil ECG at 480 milligrams, the high of the prescribed dose level, and diltiazem 350 milligrams. Dr. Jeff Anderson and Jim Reifel and Al Waldo, all three, described each of these ECGs as definitely abnormal among certain significance in terms of the T and U-waves.

DR. DiMARCO: What about dispersion? This is one of the things you could reconcile even if you believe these are QTs or something. Some people would say that dispersion is measured by taking the notch between the TU and if you saw no change in dispersion, that would be

reassuring, whereas the other drugs would show a change. Did you look at that?

DR. KOBRIN: We didn't look specifically on dispersion in the clinical studies you have shown before -- Dr. Tomaselli showed you before. We looked at these in the preclinical studies where there was no discussion at all, while with the other drugs, there was a big dispersion with regard to the action potential. In the clinical studies, we didn't look at it.

DR. MASSIE: We're going to have to take a break I think, but resume this discussion shortly thereafter. So, 11:15 promptly, and then we're going to start again with the questions.

(Recess.)

DR. MASSIE: Could everybody please take their seat right away? We're going to continue the discussion.

Dr. Kobrin? Dr. Kobrin has a comment and then we'll start continuing with the questioning.

DR. KOBRIN: What I want to do is just to clarify one point that I think maybe we didn't explain well.

When we looked at the ECGs of mibefradil, verapamil, and diltiazem, the morphological changes that we have seen were similar when we looked at the highest

recommended dose of mibefradil, verapamil, and diltiazem, and the major changes we have seen at twice the recommended doses of both drugs.

So, it's not that we have seen these changes on mibefradil normal doses and on these drugs on supratherapeutic. It was the same proportion, twice the recommended doses and at the highest recommended doses that we have seen the same changes. And this was confirmed blindly by the three experts who looked at these ECGs.

DR. MASSIE: Thank you. Good.

We'll go from left to right for questions.

DR. KONSTAM: Well, I just have one question that Dr. DiMarco warned me against asking, but I'm going to ask it anyway.

What's your thought about the electrophysiologic explanation for the ECG findings that we do see?

DR. KOBRIN: What you're asking is what is the reason for seeing these changes?

DR. KONSTAM: Yes. What's the electrophysiologic explanation for it?

DR. KOBRIN: The point is this. We looked into this issue and there is a very interesting explanation, that these changes could be related to the decrease in the

action potential. Dr. Noble is with us and I think it will be a good opportunity if he can show two or three slides to show how shortening of the action potential can result in morphological changes, if it's okay.

DR. NOBLE: Yes, thank you very much.

The question we have looked at and tried to answer is how it can come about that changes in action potential duration of the kind seen with mibefradil which consist at therapeutic and even several times therapeutic levels in very modest shortening of the action potential can nevertheless result in ECG changes that resemble those that would be produced by action potential prolongers.

The essential answer is that it's wrong to think that being a unique relationship between the action potential duration change and the change in the morphology of the T and U-wave. The way in which we've tried to answer that is to use a computer model. It's a very realistic computer model, and if I can have carrousel 43, slide 1, I'll start by explaining how the model has been put together.

The model is based on taking first an anatomically realistic model of the canine heart. Here it is in cross section, here in vertical section. It has got anatomically realistic properties, and to those anatomical

properties are added the basic electrophysiology of the action potential with a variety of models.

What you end up with, of course, is a model of huge proportions. You need massive computing power to do this, and the team that has done this has used a 12-processor power challenge to the graphics computer at the Johns Hopkins University here in the United States under the direction of Dr. Ray Winslow, and I am the consultant.

What you're seeing here is, first of all, a validation of that model using the activation isochrones that it generates as you activate the spate of excitation through the model in a way that resembles the way the Purkinje network normally activates the ventricular mass.

The main take-home message here is that if you compare that data from the simulations against 240 electrode epicardial recording systems in the dog heart, they correspond. So, there's a good reconstruction of the normal sequence of activation through the ventricles.

Now, the key question is this. How can it come about -- and I should add, of course, that if you immerse this model heart into a medium where you compute the electrical changes that would occur outside the heart in the solution surrounding the heart -- in the volume conductors surrounding the heart, you can of course compute

the electrocardiogram and you can do that for all leads.

Now, if we go to slide number 2, we'll go directly to the question that is of relevance to the mibefradil result. The question is, how can it be that a drug which at relatively high concentrations produces shortening of the action potential with a tendency to produce, as you've seen from the basic data, a shortening that is greater at the top of the action potential than at the bottom -- how can that proceed to produce a flattening of the T-wave?

So, the simulation which has been run here -- this is one of many simulations that have been run -- is to take this as the normal repolarization phase of the action potential and to simulate the mibefradil result with this change as the changed repolarization. You'll notice there's a bigger effect at APD50. That's the action potential repolarization time for 50 percent repolarization, and in fact in this particular simulation, there's a 0 change at APD90.

Here are the T-waves that are produced first by the controlled repolarization, and that is this big T-wave here. Then as you shorten the action potential, in this case only by around 2 percent, you achieve something like a 25 percent reduction in the T-wave amplitude, and you'll

notice also that it spreads out.

Now, that means that it is relatively easy to produce a T-wave change with an action potential shortener that closely resembles what would happen with action potential prolongers. So, how can that be? How can you have the same or very similar T-wave changes produced by very different effects on the action potential?

And the answer is the clue that I gave at the beginning of my presentation, which is that there is no unique relationship between action potential duration and the form, amplitude, and duration of the T-wave. You have to take into account also the form of the action potential, and you also have to take into account the dispersion of those forms of action potential throughout the myocardium.

There is no reason, therefore, why both action potential shortening and action potential prolongation should not in the end produce the same end result which is a reduction in the peak gradients but a spreading out in the duration of those gradients. If you achieve that result, you will get a result that is very similar to that observed with mibefradil.

Moreover, if there were latent in the system a mechanism that corresponds to the late production of a U-wave -- we're hypothesizing in this case that in the normal

circumstance before the T-wave is flattened and moved in, that there is latent within that a U-wave basis -- then there is no reason why that shift and flattening should not start to uncover a U-wave mechanism.

That doesn't answer the question what the U-wave mechanism is, and I can go on on some of that kind of question if the panel wishes me to do so.

But I think the essential take-home message, what I'm saying here, is that there's no real puzzle as to why mibefradil, producing action potential shortening of the kind that we've seen in the electrophysiology, should not produce the T-wave changes that are seen in the clinic.

I must add to that too that there would be a great surprise if other L-type calcium channel blockers like verapamil did not do the same. So, we were delighted after running these simulations, to find from La Roche data that indeed verapamil and other L-type calcium channel blockers do produce the same effect. Why this hasn't been noticed before in the clinic is a question which eludes me because to me it's very clear that these effects should occur, they're necessary.

DR. DiMARCO: What if you ran an IKr blocker that prolonged the action potential?

DR. NOBLE: I'm sorry. The acoustics here are

terrible. Can you repeat that?

DR. DiMARCO: Yes. If you ran something that prolonged action potential duration --

DR. NOBLE: Yes.

DR. DiMARCO: -- what changes would you get on the cardiogram using your model?

DR. NOBLE: Yes. It will depend entirely on how you prolong the action potential duration, just as it depends entirely on how you shorten the action potential duration. So, it depends on what form change you introduce into the computations.

With action potential prolongation and with action potential shortening, you can achieve either an increase in the peak of the T-wave or a decrease of the peak of the T-wave simply depending on whether the form of action potential change that you simulate reduces or increases the gradients of repolarization. It's the dispersion of repolarization producing gradients of voltage during the T-wave that generate the intensity of the T-wave.

But to answer what I think you're leading up to, would there be any differences between what would happen if you put in an action potential prolongation producing a lowering of T-wave and an action potential

shortener producing a lowering of T-wave, the answer is yes. The tendency will be, as in these simulations, for the peak of the T-wave to move in with action potential shortening and to move out with action potential lengthening. That's consistent with the fact that, if anything, the peak of the T-wave in the mibefradil results tends to move in rather than out. That would be the key difference.

DR. MASSIE: Ray?

Thank you very much, by the way, for that information.

DR. LIPICKY: Just a couple of questions I guess. I should know the answer to the first question I'm going to ask.

This is a conducted action potential?

DR. NOBLE: Yes.

DR. LIPICKY: So, does altering the action potential duration alter the conduction path? Is that what's going on?

DR. NOBLE: Not in itself, no. In these such simulations, it assumed that the activation pathway is unchanged, and that I think is reasonable given that there's no evidence that mibefradil alters the sodium channel. It doesn't seem to alter the Q-R-S complex. So,

we've naturally assumed that the conduction pathway for depolarization remains unchanged.

DR. LIPICKY: Okay, but there is no evidence that mibefradil does not alter the sodium channel.

DR. NOBLE: There's no evidence that it alters the Q-R-S complex, and I think it would be very difficult to imagine -- if there were an effect on the sodium channel, we would certainly expect to see some change in the Q-R-S complex.

DR. LIPICKY: How sure are you of that statement?

DR. NOBLE: Absolutely positive.

DR. LIPICKY: All right.

(Laughter.)

DR. MASSIE: Moving down the row, Cynthia, you had a question I know earlier.

DR. RAEHL: Yes. This is a biopharm question first and then I'd like the reaction of Dr. Ruskin, please, or Dr. Pratt.

The basis of my question is some of the drug interaction studies and looking at the common metabolic pathway of this drug and some other common drugs such as quinidine, perhaps even terfenadine. My question is, if in the study that's cited in the FDA review, that we saw an

AUC increase in quinidine of about 50 percent. I can't tell from the review if that's a single dose, 400 milligram per day study, or 400 milligram q.i.d., or whatever.

My question is, do you have any further biopharm data that would give me some sense of comfort what would happen if these two drugs are administered concomitantly? My definition of a high risk population. So, I'd like both a biopharm response first and then a clinician's response.

DR. KOBRIN: Let me answer this question. Due to the fact that mibefradil interferes with the metabolism of terfenadine and for the same reason with astemizole and cisapride, we are planning to recommend contraindication of the combination of mibefradil with these three drugs.

DR. RAEHL: Absolute contraindication.

DR. KOBRIN: That's right.

DR. RAEHL: Dr. Ruskin and Dr. Pratt?

DR. RUSKIN: I have nothing to add to that. I'm not privy to the details of those data, but I think it sounds like a cautious approach.

DR. MASSIE: Those are the only three drugs that you are going to be recommending absolute contraindications to?

DR. KOBRIN: These are the three drugs that we

expect that, if they will be given with mibefradil, their concentration will increase. As a result, it can affect the QTc and we might see proarrhythmic effects. Therefore, we would recommend to contraindicate this combination.

Regarding quinidine, we have a single-dose study where we have seen some increase in quinidine concentration, but also a decrease in the active metabolite, and overall the change in QTc was small. Currently we are running a study with multiple dose quinidine, and we will handle it in the package insert.

DR. RAEHL: Any data with concomitant administration of amiodarone? Are you conducting any studies such as that?

DR. KOBRIN: We don't have interaction studies with amiodarone.

DR. MASSIE: But there is amiodarone in MACH 1.

DR. KOBRIN: Yes, there is amiodarone in MACH 1, and also in the pilot CHF study, we had several patients on amiodarone, but it's too small to come to a conclusion. But definitely we will know from MACH 1 what is happening.

DR. MASSIE: Those weren't any of the four with sudden death?

DR. KOBRIN: Excuse me?

DR. MASSIE: Of the four sudden deaths, were

any on amiodarone?

DR. KOBRIN: One.

DR. MOYE: I have a question for my fellow committee members. Now, I understand that this right usually falls in the purview of Ray or Bob, but I'd like to ask it anyway because I am concerned that we are making a decision here with important public health ramifications with less than minimum data, and I need some guidance here if I'm wrong.

As I absorb what we've heard this morning, these researchers in a very rigorous fashion and in controlled settings -- that is to say, controlled doses -- have identified something odd about the ECGs for some patients who take this medicine. We've heard this morning arguments for and against QTc changes versus U-waves, but something strange is going on.

We've also seen some pilot data which shows numerically more sudden deaths in mibefradil, nothing statistical, and so maybe I don't feel bad about that, but I sure don't feel good about what I've seen.

If approved, the market that will be available for this drug will be essentially uncontrolled. We'd like to believe that the physicians who will eventually prescribe this would follow the precise recommendations

laid down by the sponsor, but that probably will not be the case. Patients will be taking this in fairly uncontrolled situations in combinations of drugs which have ramifications yet unknown.

I just wonder, aren't we obligated to provide some assurance that the ECG changes we've seen here today are not ultimately lethal? And wouldn't some of that assurance be provided by waiting until the end of the heart failure trial?

DR. MASSIE: I don't know whether that's a question that we should discuss or keep in mind as we discuss other questions at this point in time. If you don't mind, Lem, we'll sort of keep it in mind, but I think that's clearly going to come up as we try to answer the questions in the protocol.

Although you did raise one point I'd like to follow up on. Your electrophysiologic studies in human subjects, they were normal subjects. Is that correct?

DR. KOBRIN: As I've shown, they were normal in respect to specific things, but most of them came to the electrophysiology because of either arrhythmic events or post-radiofrequency ablation, most of them. Many of them had ischemic heart disease and some of them had congestive heart failure.

DR. MASSIE: Do you have planned or are you conducting any studies in patients who manifest this Q-T-U phenomenon?

DR. KOBRIN: What kind of studies you are talking about?

DR. MASSIE: I'm not sure who might volunteer for such a study.

(Laughter.)

DR. MASSIE: But it would certainly be reassuring if one knew that in the patients who develop these types of repolarization changes, that they were not more likely to be induced into polymorphic ventricular tachycardia.

DR. KOBRIN: What we know is the following. We do have on our database quite a number of patients at the supratherapeutic doses who develop these T-U morphological. We looked specifically into these patients to see if there are any events or anything that might indicate that there is a problem, and there was nothing.

We looked at the patients who had events to see if they had T-U morphological changes, and the answer is for most of them, no. In fact, at the recommended doses, we can hardly find these cases. The incidence is small.

Let me also add one more thing for what Dr.

Moye said. The four sudden deaths that we have seen in the pilot study -- we also were concerned about this, and this is why we informed the Safety Committee of MACH 1. If this observation was true, this would be reflected in MACH 1 and the study would have been stopped much earlier I think if this is true.

Now, we looked specifically into these cases. None of them had these changes. They didn't have prolonged QT. They didn't have any reason to believe that it is connected to the drug and we think that this was a chance finding. In the same study, 4 weeks follow-up, which is the routine in our studies, there were two deaths on the placebo group and none on the high dose group, which means that when you have a high incidence of death rate, it can change from month to month. We think it's a chance finding. MACH 1 is our way of looking at these. Most probably this numerical imbalance is a chance finding.

We feel comfortable with the fact that the Safety Committee recommended to continue the study knowing the results, knowing the TU, knowing the concern of the FDA. So, this is an alerted Safety Committee.

DR. MOYE: I understand that, and that's why I said when I spoke about the pilot data, I can't say I really feel bad yet because, as you say, it may be just a

play of chance here, but I sure don't feel good.

The notion about what the DSMB says, I don't get much solace there and I'll tell you why. What we require is the most specific, the most sensitive information about these findings in the trial, and they are obligated from their point of view to give us the most general information. So, it is better than nothing, but not much.

DR. MASSIE: JoAnn?

DR. LINDENFELD: I just have a couple questions.

In the patients in whom the electrophysiologic studies were done and the effective refractory period was normal, do we know the doses or the duration of treatment with mibefradil and do we know if any of those had this ECG abnormality?

DR. KOBRIN: You're talking about the electrophysiology study?

DR. LINDENFELD: Yes.

DR. KOBRIN: This was a single IV dose where we gave a bolus and a maintenance dose to reach specific plasma concentrations. So, overall there were about 1 hour on infusion, and during this time, they were exposed to mibefradil. They didn't get any mibefradil after.

DR. LINDENFELD: Did any of them have the ECG abnormality we're talking about?

DR. KOBRIN: They didn't have any changes.

DR. LINDENFELD: Given what we've heard, I'm wondering if you have thoughts -- and this addresses all of you I think -- about the need for a screening ECG before treatment with mibefradil and then follow-up ECGs as a routine part of therapy with this drug?

DR. RUSKIN: I've thought about that as well and my reaction to that is that I would not be inclined to do it. That's based on I think my conviction that this drug behaves like two other calcium blockers that I use a lot and that I'm comfortable with electrophysiologically. I don't see with doses of 50 and 100 a logic behind requiring screening EKGs and EKGs on the drug.

DR. LINDENFELD: We might have other people comment on that.

Do you have any idea of drugs which prolong the QT interval that are commonly used, what percentage of patients that would be candidates for mibefradil would be taking those drugs? Just approximately. 1 percent, 10 percent? In other words, what percent of the population we're thinking about treating would be on drugs which prolong the QT interval?

DR. RUSKIN: I don't know an answer to that. I'd be happy to yield to anyone who can offer you one, but I would like to perhaps respond with a comment and that is that I don't know that I would be particularly distressed by the concomitant use of this drug with a drug that prolongs the QT interval. In fact, this group of drugs, particularly verapamil, is used in some centers to treat long QT syndrome. I would be concerned where this drug interferes with the metabolism of a drug that increases the QT interval.

DR. LINDENFELD: Right, exactly.

Do you have any idea what percentage that would be?

DR. RUSKIN: I don't.

DR. LINDENFELD: Small, medium, large?

DR. RUSKIN: Not even a clue, not a clue.

DR. LINDENFELD: Then I guess in that same vein, I'm also concerned about the cyclosporin interaction. As I understand it from the manual, there are two to threefold increases in cyclosporin levels which I think, while not affecting the QT interval, could be quite dangerous. Is that correct? Is that correct information?

DR. KOBRIN: It is correct that there is --

DR. LINDENFELD: And that would hold for

Prograf as well then probably, although we don't have that information.

And that could be quite a dangerous interaction, I think, increasing cyclosporin levels two and threefold.

DR. KOBRIN: As we all know, the cyclosporin levels are being monitored when it's given, and if it's high, it is reduced. The administration is followed based on plasma concentrations, and if these drugs are being given, there will be a need to reduce the dose of cyclosporin and of course to follow it, but it's not contraindicated.

DR. LINDENFELD: That's true but there's a wide range around two to threefold, and as we've all seen, sometimes you get the cyclosporin level back before -- you know, a very high level. In other words, two to threefold increases could produce seizures in patients.

DR. KOBRIN: Maybe our pharmacokineticist can answer better than I can.

DR. BULLINGHAM: Roy Bullingham, clinical pharmacology.

I think you mentioned FK506. I think you're right. There would be a similar type of response with FK506 to what we see with cyclosporin.

I think in the label the issue of the increase being two to threefold would be addressed. I think in regard to this matter, you should remember that use of some drugs like ketaconazole is actually done deliberately so as to reduce the dose of cyclosporin.

DR. LINDENFELD: But that magnitude is not two to threefold.

DR. BULLINGHAM: With ketaconazole it's two to threefold.

DR. LINDENFELD: Isn't it about 50 to 100 percent with diltiazem? 50 to 100?

DR. BULLINGHAM: I think it's more with ketaconazole.

DR. LINDENFELD: Around the range of two to threefold. What is the range? In other words, the mean is two to threefold. Do we have a range here that's 2 to 6 or 2 to 8?

DR. BULLINGHAM: No. Actually the upper end is threefold. The lower end is a 25-30 percent increase.

DR. LINDENFELD: The manual sort of implies, though, that the mean is two to threefold. Is that misstated?

DR. BULLINGHAM: I believe it is in terms of the AUC increase. The mean AUC increase was actually

somewhere around about 1.5, but it went up to two to threefold.

DR. MASSIE: I just have one quick question. You had a diuretic background study and then I assume during your long-term follow-up there are a fair number of patients who are on diuretics in the hypertension population. Do you have an incidence of hypokalemia that you would be aware of in that group of patients?

DR. KOBRIN: We didn't have cases of hypokalemia at high incidence. But what we did, we looked at patients according to their potassium level, taking patients with potassium levels falling below 3.8 and below, 3.5 and below, looking at what happens to the QTc, and if there was anything, it decreased.

DR. MASSIE: Okay. Thank you.

Ralph.

DR. CALIFF: I think most of the issues have been covered. It was an extraordinarily clear presentation that I think took the key issues head on. I have one factual issue I just want to make sure I have right.

If you take patients in controlled trials right now in your database, at least by my calculations, you have eight deaths in the patients treated with mibefradil and one death in the either placebo or control populations. Is

that correct?

DR. KOBRIN: In the controlled studies, there were 2 deaths out of 2,000 for mibefradil and 1 in 1,000 in the comparators, either placebo or comparator. In the long-term safety angina study, there were 4 deaths and none in the hypertension long-term safety study. There were a few additional deaths after the study was completed within 28 days of follow-up, and at this time point these patients were on all kinds of different other treatments. So, what I've shown you before, which was the 6 deaths, was during active treatment.

DR. CALIFF: No, but I'm talking about the entire database, including the heart failure trial, during the period in which patients were either on mibefradil or controlled treatment. It looks like 2 versus 1 for hypertension and angina and 6 versus 0 in the heart failure trial. I just wanted to make sure that that's correct.

DR. KOBRIN: That's correct if you include the pilot heart failure in the angina and hypertension database. We specifically put it away because it's related to a different indication and we are seeking this indication in the MACH 1 which is our comfort level regarding the specific pilot studies that we have seen.

DR. CALIFF: I don't want to be taken

incorrectly on this. I congratulate you on taking on directly addressing the LV dysfunction group. It's a critical thing and I wish more companies had done this as part of their development.

But on the other hand, we all know that in the real world of treating hypertension and angina, at least half the patients with significant LV dysfunction have not even had a measure of LV function by the practitioner treating the patient.

How many patients in your hypertension or angina studies had left ventricular dysfunction?

DR. KOBRIN: Well, we didn't look for this parameter in an ongoing basis. Patients with symptomatic congestive heart failure were not allowed into these studies and we are studying this specific issue, as I said, as part of our congestive heart failure program. I don't have data on the hypertension and the angina patients regarding left ventricular dysfunction. I would assume that some of them probably had left ventricular dysfunction, but I don't know how many.

DR. CALIFF: I guess it would maybe help me just to know how -- I don't think we have all the inclusion criteria from the protocols, but was there an effort made beyond symptomatic heart failure to screen out patients who

might have had a previous MI or other markers of LV dysfunction?

DR. KOBRIN: Patients with previous MI were not excluded and only overt congestive heart failure was excluded. By the way, regarding the pilot study, the recruitment was 2 to 1 for mibefradil versus placebo. So, it's twice as many patients were on mibefradil than on placebo in the pilot study.

DR. CALIFF: Right.

One last question. This is a hard question I know, but I feel like I need to ask it. Do you think that therapies for angina and hypertension should be evaluated somehow without considering the overall potential for those therapies to affect mortality given that the populations being treated are going to include a heterogeneous mixture of patients with and without LV dysfunction?

DR. KOBRIN: What exactly is the question? Is the question if we need a mortality study in this indication?

DR. CALIFF: Are you really comfortable that with so little mortality data in sort of the below-the-surface large population of patients that it's safe?

DR. KOBRIN: I think that with the information that we have -- and we have to look at it as a whole --

looking at the preclinical data with the shortening of the action potential, looking at the electrophysiology data, looking at the clinical database, including MACH 1 and the phase IIIb that are going on, I think it gives us the same comfort level as one would see with other NDAs at this stage.

I think that the mortality study in patients with hypertension and angina pectoris is something that definitely would be nice to have with any drug after being released to the market. I think that a lot of drugs are reaching this point.

It's very interesting that we decided to go into the MACH 1, the mortality study, very early based on a lot of evidence from preclinical, especially from preclinical, and clinical studies that there is a good chance that this drug might be an effective drug for patients with congestive heart failure. So, this is why we started it early in the program and it will be finished I hope soon.

DR. KONSTAM: Could we get the denominators on those numbers that you just gave? You said 2 out of 1,000 and 1 out of 1,000 in the hypertension and angina and 6 deaths in the heart failure population, none in the placebo. Just what are the denominators on those? Can we

do it without showing a slide?

DR. KOBRIN: Okay. It's coming from all controlled studies, the placebo and active-controlled. There were 1,000 patients on placebo and active-controlled and 2,000 patients on mibefradil.

DR. KONSTAM: In hypertension and angina.

DR. KOBRIN: That's right. So, it's 1 in 1,000 and 2 in 2,000.

DR. KONSTAM: Right.

DR. KOBRIN: In the safety follow-up --

DR. KONSTAM: Right. No, I got that. In the heart failure. You mentioned there were 6 six deaths in the controlled heart failure population.

DR. KOBRIN: That's right.

DR. KONSTAM: What's the denominator there?

DR. KOBRIN: 160 patients on mibefradil and 80 patients on placebo.

DR. KONSTAM: And no deaths in the 80.

DR. KOBRIN: Not during the study. There were two deaths on placebo after the study within 28 days follow-up.

DR. KONSTAM: So, it's 6/160, 0/80.

DR. KOBRIN: Yes.

DR. KONSTAM: Thank you.

DR. MASSIE: Ray and then Cindy.

DR. LIPICKY: I would like to, just for the sake of -- as you're discussing things, there's a perspective that I think I'd like you to think about, and while the transparencies are coming up front, and you can put overhead number 5 on.

I'm not sure that looking at the results of reasonable reassurance, and let me offer this for your thinking process and that is let's give mibefradil a 20 percent treatment effect in congestive heart failure, and let's say that treatment effect is on mortality. Let's say that there is a 1 percent induction of torsades and half of them in fact die. MACH 1 would look pretty good. So, if one is looking for evidence that the things we've been talking about are not significant, I don't think you can look in MACH 1.

The second thing is this curve that was in the stuff that was sent to you. On the x axis is the dose of mibefradil. On the y axis on the left-hand side is the QT, and the little horizontal bars are the mean QT at some collected dose and then the limits. So, the longest QT increased 34 down and so on. Then the hatched line is the points drawn through the estimates of the effect size, here for change in ETT on exercise tolerance. Okay?

Now, there are confidence limits that go both upward and downward vertically and left to right, because these are all estimates of dose and so on and so forth.

So, it looks to me that this effect on S-P interval is just beginning to enter its dose-response relationship, and it looks like the therapeutic dose-response relationship is a little to the left, but it would pretty much overlap if what you did was put the confidence limits around it. Okay? Because there have to be confidence limits in the x direction also.

Put up the overhead 4.

DR. CALIFF: Not carrousel number 45?

(Laughter.)

DR. LIPICKY: Well, it's actually in carrousel 128.

(Laughter.)

DR. LIPICKY: But I left it at home.

(Laughter.)

DR. LIPICKY: This is the same thing for lowering of blood pressure. Now, this is a very deceiving slide. The QT stuff here comes from one study, the one study where in fact it became apparent, and the mean effects are coming from averages of all studies.

So, I don't mean to say this is reality, but to

me as I look at these things, if you put confidence limits around the curves, there's a lot of overlap. So, when one is talking about suprapharmacological and big doses, those terms don't have a lot of meaning to me. And I just want you to keep that in perspective as you talk.

DR. MASSIE: Bob?

DR. TEMPLE: Ray, were those confidence intervals you were showing or maximum and minimum?

DR. LIPICKY: For the QT it was maximum and minimum.

DR. TEMPLE: One can read those as saying that between 6.25 and 200, there isn't any change. What makes you say there is?

DR. LIPICKY: Yes, and then everything that everyone has been talking about is a non-phenomenon.

DR. TEMPLE: That's what I'm asking. Is that what you're showing or not?

DR. LIPICKY: You must accept that the phenomenon that's being discussed is real -- no one disagrees with that -- and that something happens to the S-P interval as a function of dose of mibefradil.

Now, granted that you can look at some aspects of this data that would deny that statement. There's no question about that. And then you can also look at aspects

of animal pharmacology, single cell pharmacology, and so on and so forth that say that's somebody else's problem.

So, I don't think that slide was put up to establish the phenomenon. The phenomenon has been discussed for the last hour or hour and a half, and everyone that has looked at it agrees it exists. The slide was put up only from the vantage point of what confidence one can have that there is the large separation and what suprapharmacological means in that context. And that's the only reason I showed those overheads.

DR. TEMPLE: I was trying to find out what those overheads were intending to communicate. For example, the one looking at angina makes it look as if -- the only points that are there -- that whatever the maximum response is occurs at 100 milligrams, and the little bit of data above that didn't show anything.

But what I don't understand, apart from what we've heard all along, where people agree that there's a Q-U phenomenon -- and you've gone some way to explaining that that's a morphologic change. It wasn't clear what you were trying to convey in that slide about the Q-U response, whatever that means because the numbers all look the same all the way from left to right.

DR. LIPICKY: Well, but that's fine. If that's

how it looked for you, then what I said had no meaning, and I just threw it out so that people could look and decide whether what I said had meaning or not.

DR. MASSIE: Well, let me just ask a question about that. I may have missed this in my notes, but I thought when Dr. Kobrin was presenting, there was a 4 percent incidence of this phenomenon at the 100 milligram dose.

DR. KOBRIN: That's right.

DR. MASSIE: Where did that appear on Dr. Lipicky's --

DR. LIPICKY: It didn't.

DR. MASSIE: How come? Wasn't that the highest? Wasn't the 36 millisecond point and 100 -- wasn't that the highest increase in the --

DR. LIPICKY: Can I retract everything I said?

(Laughter.)

DR. LIPICKY: It is not worth going any further with it because what I thought those things meant obviously is confusing everything and it does not contribute that much to the discussion. I thought it might help the discussion.

DR. MASSIE: Let me then turn around and make sure I'm correct on that 4 percent number. Didn't you say

that 4 percent of patients treated with the 100 milligram dose had this abnormality of Q-U interval or change?

DR. KOBRIN: That is correct. As I said, at the upper quartile,it was 1 percent on 50 milligram and 4 percent on 100.

Again, I thought that we agreed that the issue is not intervals, and I think what the slide was showing is intervals rather than the phenomenon.

When we are dealing with the phenomenon, I think that we have to look at it and say is this phenomenon something that worries us or not and I think that this is where we are looking at the whole picture and saying that this is a drug that lowers the action potential and, as a result of it, could cause these morphological, this is a complete difference from drugs that prolong action potential and can cause maybe sometimes similar morphological change but also prolong QT. And mibefradil does not prolong QT.

DR. MASSIE: I think I understand my confusion about the issue. It's a change in morphology that wouldn't be necessarily reflected in measurements of milliseconds.

DR. CALIFF: Barry, I just want to be clear that my concern is entirely different. I'm glad you all are so worried about the QT interval but I haven't found

anybody who can tell me what to do with a particular QT interval based on evidence in a particular patient.

I've been convinced reasonably well by what has been shown that this drug acts on the EKG more like verapamil and diltiazem which we know are not good for people with impaired left ventricular function. I don't know why that is but it's an observed phenomenon in large clinical trials that has been pretty clearly detected.

It has been a great presentation to allay a lot of my concern about the QT interval issue, but I'm concerned about another issue which should be kept distinct I think.

DR. GRINES: I echo Rob's concerns and specifically if you look at the slides I think that were provided by Dr. Kobrin on safety on the pilot CHF study, it seems like the mortality rate is approximately 8 percent versus 0 percent with the placebo or 0 percent using a lower dose of the drug.

Another question I have relates to slide 20 in which they calculate the mortality during the placebo-controlled trials, and I wondered what that mortality would look like if it was, in fact, confined to only patients who were going to receive the recommended dose of the drug.

Then secondly, I'm a little bit concerned about

these placebo-controlled trials only having a 4-week follow-up period, and so these mortality results are from 4 weeks. If you look at the open-label study in which angina patients are treated with this drug, the mortality remarkably increases I assume due to a longer period of follow-up.

So, if we could have those issues addressed.

DR. KOBRIN: It's a very complicated question.

DR. MASSIE: Yes. One at a time. What issue?

DR. GRINES: Well, it's basically the deaths. The death rates seem quite high in the congestive heart failure pilot study if you use the recommended dose of 50 to 100. Rob has already pointed that out. And I wish that we could get the mortality rates on the hypertension and angina patients using the recommended dose, and if they could clarify what the period of follow-up was in which the mortality rate was calculated.

DR. KOBRIN: As I've shown you on the slides about this point, in the placebo-controlled studies there was one death and this was at an under-therapeutic dose, which was at 12.5 milligram in an elderly woman, because of mesenteric thrombosis. These were at all doses including the high doses.

In the comparative studies where we used the

recommended doses, there was one death on mibefradil and one death on a comparator.

In the long-term safety study in patients with hypertension where patients were exposed to a period of 6 to 12 months to the drug, to the recommended doses, there were no deaths. There were 4 deaths among the angina patients who were exposed to the drug for 6 to 12 months, and none of these patients could be regarded as drug-related, as I said before. There was one sudden death after 300 days. The death rate among these 450 patients is not unexpected in this patient population.

I still think that the pilot study by itself is a concern, but this is why we have MACH 1 that makes us feel comfortable that what we have seen in the small study could be a chance finding.

DR. MASSIE: Just one more time. The other 3 deaths in the long-term phase. One was sudden and what were the other 3?

DR. KOBRIN: There were two cases of myocardial infarction and one case of epiglottitis that probably resulted in myocardial infarction.

DR. GRINES: Thank you.

One question for Dr. DiMarco. There has been a lot of discussion about the action potential duration as a

surrogate for proarrhythmic effect, and I wonder how convinced we are that lack of prolongation in the action potential indicates the safety of a drug.

DR. DiMARCO: Well, my feeling is that the drugs which have been associated with drug-induced polymorphic ventricular tachycardia do, indeed, usually prolong the action potential duration. In fact, I think all of them do.

There are other types of proarrhythmia that can be fatal that are not reflected in action potential duration, but I see no indication that this drug has that in its profile.

I do share the concerns that have been expressed that there are in patients with congestive heart failure from drugs like verapamil and diltiazem certain studies which have shown increased mortality, and as you know, the mechanism of that mortality is never really worked out. And whether that's proarrhythmia in the classic sense or whether just an increase in mortality I think is hard to say.

So, I am fairly comfortable with this profile, that it is different than the drugs we usually associate with the classic action potential duration-prolonging proarrhythmia pattern. Is that a close enough answer?

DR. MASSIE: Marvin.

DR. KONSTAM: Can I just ask a couple little questions?

Just a minor question. This pilot group of randomized heart failure patients, 160 and 80 -- were they on background therapy of ACE inhibitors?

DR. KOBRIN: They were on background therapy of diuretics, digoxin, and also different kind of other drugs, including anti-arrhythmic drugs.

DR. KONSTAM: So, they were all on ACE inhibitors.

DR. KOBRIN: Most of them. Those who could take it, yes.

DR. KONSTAM: When is MACH 1 going to be completed?

DR. KOBRIN: When we will reach 669 deaths and this is estimated to be summer of next year.

DR. KONSTAM: Summer of next year.

I know we've seen the data from the statistician, but if you could give a simple answer. Is there a simple answer to this? What's the maximum excess mortality that could be present based on the current database without having stopped it? Is there a simple answer to that?

DR. KOBRIN: I don't think that there is a simple answer. I think that Dr. Norbert Neumann has shown you that if there would have been an excess of 23 deaths, we would see that the committee is alerted. They would ask more information, more data. But we don't know if this is true. We are assuming it.

DR. KONSTAM: What percent excess would that have been?

DR. KOBRIN: Norbert, can you answer that?

DR. NEUMANN: As I showed in the good direction -- in the bad direction, an excess of 33 percent would cause stopping of the trial. It would be 107 deaths in placebo and 161 in the mibefradil group. Then they would reach the O'Brien-Fleming boundary and they have to stop the trial according to the protocol. That is for efficacy and for safety sake, where they have to stop the trial.

As I said, we have alerted the committee and we expected even earlier a signal that we have a problem.

DR. KONSTAM: But they might or might not have communicated that. I guess it sounds like the only thing we're pretty darned sure of is that there is not greater than an excess of -- what did you say -- 33 percent mortality -- 33 percent excess. That's the thing of which we can be very confident.

DR. MOYE: I think we're sure that there was neither a therapeutic triumph nor a therapeutic catastrophe.

DR. KONSTAM: Right.

DR. MOYE: That's all we know.

DR. KONSTAM: I just want to get an idea of the quantitative magnitude.

DR. KOBRIN: But we also have to be very clear about this again. I'm not on the Safety Committee, and knowing what they know and being asked to look specifically into arrhythmic and potentially arrhythmic deaths -- and they looked into this, and they still informed us, go on as planned.

DR. KONSTAM: So, you think you would have known it at a lower level then, some lower level. You think they would have alerted you.

DR. KOBRIN: I think that if they had a problem, they would ask earlier interim analysis or additional data or additional information.

DR. KONSTAM: Thank you.

DR. CALIFF: Well, I have to respond to that being involved in a lot of these kinds of trials. I think that's a very difficult decision for an independent committee to make because alerting a company of a potential

problem when you're not going to stop the trial can create an incredible mess in terms of people knowing all kinds of things about what's going on in the trial. So, I don't think that we can take it for granted that even if there was a problem, you would know about it.

I'd also like to comment that the 33 percent point estimate being exceeded as associated with confidence intervals, it could go well beyond 33 percent. In other words, if you hit 33 percent, the trial would be stopped. That estimate would have confidence intervals that might be up to maybe 60 percent.

DR. KOBRIN: Maybe Dr. Norbert Neumann can answer that.

DR. NEUMANN: May I have carrousel number 41, slide number 24?

DR. MASSIE: I'm not sure we really need to go much beyond that. We know that the effect for sure has to be quite substantial.

DR. NEUMANN: I had made a calculation of the confidence interval. As a basis I had assumed the 10 percent given in the protocol and a 95 percent confidence interval. Given what I said, a liberal assessment would be the upper 95 percent limit, a 47 percent increase in relative risk. I think as a statistician in a safety

assessment, I use normally for a safety assessment a p value in a range between 10 and 20 percent, in contrast to an efficacy assessment.

I also calculated this for a conservative approach with 20 percent, and I think we have to have in mind this committee was alerted to the findings of the agency. The upper bound would be 95 -- the upper 95 there will be 45 percent.

DR. MASSIE: Lem and then Mike.

DR. MOYE: Craig, you're going to be surprised to hear these words out of my mouth. Do you think that the DSMB would be receptive to an unprecedented request from the FDA to provide the unblinded data under prearranged assurances of confidentiality? Would that be worth entertaining?

DR. PRATT: Well, let me say that this will be a personal opinion. I don't represent the company in this.

I know that everybody on the committee -- having sat there for a long time, I too would like to know a lot more about the MACH 1 data.

There's also a tremendous belief within the company and with the experts that designed this trial that there's still a possibility of benefit because there are differences between this drug and verapamil and diltiazem.

So, there has been a tremendous interest in not doing anything to jeopardize it.

So, that's kind of the hard line, and we sit here suffering. Yet, if there was some way, to my way of thinking, that reasonable people could sit down and say, listen, we want the results of this trial, we want this trial to be completed, it was an important trial, the company did the right thing in the first place, and yet we'd like to get more information to deal with this very piece of unknown, if that's a possibility, I would love to see that happen personally. But I don't want to speak for Roche.

DR. KOBRIN: We don't have any access to these. I think that the only way, maybe the FDA can find out what is going on. We have no access to this issue.

DR. MOYE: Bob or Ray, have you ever done anything like that?

DR. LIPICKY: I want to say what I said before. It would not answer the relevant questions for me. So, I see no reason to put the trial in any kind of jeopardy.

DR. CALIFF: You have a different question than we have.

DR. MASSIE: Yes, there are two questions. Rob is raising the question about safety in heart failure, and

you're saying that nothing in this trial would necessarily tell you whether the general population of hypertension patients is at risk for some infrequent phenomenon.

DR. LIPICKY: Well, that is correct. Since that is the indication being sought, the worry that some people with hypertension might have congestive heart failure and be at increasing risk is not the issue that needs to be settled.

DR. CALIFF: I have to respond to that. I'm not talking about congestive heart failure. I'm talking about left ventricular dysfunction which is present in a huge number of patients unbeknownst to many practitioners who are treating hypertension and angina.

DR. MASSIE: Bob?

DR. TEMPLE: Well, I guess it's important to find out what questions we're raising.

There are situations in which we're so worried about a drug that we insist on a mortality study before we'll approve it for symptomatic improvement. For example, you can't get a symptomatic claim in ventricular arrhythmias without providing some reassurance that you're not killing people.

If the question Bob is raising is, for calcium channel blockers, are we so nervous about what they do in

people with left ventricular function abnormalities that we won't approve them until we have this trial, that's something worth talking about, but it's worth noting that many of the drugs now approved have this problem and have been shown to. So, there's some question I think whether one would say that's a criterion for approval of an antianginal drug.

The point Ray made before, which I think is worth thinking about, is that this trial will not really reassure you one way or the other about arrhythmogenicity because you could have two distinct things going on. Some improvement in the left ventricular dysfunction, but you could still be proarrhythmic to some degree. That really hasn't been addressed. It won't really necessarily answer that question, although I guess it will rule out some devastating proarrhythmic --

DR. MASSIE: It could definitely show -- if it did show a marked increase in sudden death, and if any of those events were captured, it might show something bad.

DR. TEMPLE: Yes, it could do that. But you have a fair amount of data as to whether there is a massive increase in sudden death in the hypertensive population. It's not a controlled trial, but there aren't any deaths.

DR. CALIFF: This is a hypertensive population

screened to exclude comorbidities and other problems that we all face in everyday practice. This is a great database in people you couldn't kill if you ran over them with a truck, but it's not a database that reflects what you would see in clinical practice if you were treating hypertension or angina.

DR. MOYE: And the duration of follow-up is somewhat less, isn't it?

DR. KONSTAM: Barry? Bob, can I just respond to what you just said?

I don't see anything in the data that suggests to me that there is going to be an increased incidence of sudden death, and I think that's what Rob and Cindy were saying. I, now speaking for myself, am no longer concerned about the ECGs given what I've seen about the underlying mechanisms of action of the abnormal ECGs in drugs that cause torsades.

So, now the new signal is what Rob pointed out, is that there seems that there's a trend toward an excess mortality in a particular population in a particular dose that may or may not be relevant to the indication at hand. But to the extent that it's relevant, we would get more information from the MACH 1 data.

DR. MASSIE: We're going to have to move on to

some specific questions. Well, let's move on to these questions. These questions are quite specific and I know there are some general concerns that have been expressed and I think we should save those general concerns to the time when the general concerns are reflected in the questions and perhaps try to get the specific information from these questions as we go through them.

Again, I'll turn to our primary reviewers to address them first. As you may have noticed, there is a request that specific trials be referred to when the answers are given, and that would be helpful I think to the division.

Does mibefradil reduce the blood pressure of patients with mild to moderate hypertension? I don't think we need to vote on that, so we'll move on to question 1. What trials convince you that this is so?

Mike?

DR. WEBER: Well, in fact, we have a group of placebo studies which all show efficacy, and they're actually listed all as our figure 46 in the briefing book from the sponsor, but K13003, EC14479, BC14042, and BC14044. Now, they are done in slightly different populations, one of them being in the elderly, but they consistently show that doses of 50 milligrams are superior

to placebo and that doses of 100 milligrams are better than 50 in general, that going to 150 or 200 really doesn't add much, and that doses lower than 25 are really not separate from placebo, in one case a trend perhaps.

So, I think we can be pretty specific in answering that question, Barry.

DR. MASSIE: So, the smallest dose -- did you say 25 or you said 50?

DR. WEBER: The dose that is consistently better than placebo is 50. In one protocol, the very first one, K13003, 25 seemed to better than placebo, but that was the only time that 25 was better than placebo. So, I would say that the lowest consistently effective dose is 50 and that 100 is somewhat better than that, and that seems to show throughout these four placebo trials.

DR. MASSIE: Then the largest useful dose?

DR. WEBER: Would also be 100. 150 seems fractionally better, but truly only fractionally better. Perhaps on the very first trial, K13003, it was trending to be somewhat better, but taking a look at all studies together and looking at figure 45 which puts the different doses together so you can kind of group them, there's really no advantage in going above 100.

DR. MASSIE: So, you're answering that based on

1(C)(2), had no greater effects.

DR. WEBER: Right.

DR. MASSIE: Rather than not studied, which wasn't the case, or dose-limiting side effects.

DR. WEBER: Right, yes. That did not seem to be an issue. I think this is going to be fairly simple to describe the doses from an efficacy point of view.

DR. MASSIE: And it isn't the arrhythmia concerns that define that 100 milligram.

DR. WEBER: Right. I guess if it got down to the nuances of labeling, you could discuss whether 25 could be suggested for smaller or elderly patients if that became an issue, but to me 50 is where you'd normally start and 100 is where you'd normally finish.

DR. MASSIE: Has mibefradil been consistently more effective than alternative therapy?

DR. WEBER: That's tough because it depends on what you call consistent. Now, Ray this morning made a very strong statement about comparative trials, and for a start, there are no instances where two trials have been done comparing with one agent. So, his rule certainly has not been met.

However, in comparison with diltiazem and one formulation of nifedapine, there was superiority, apparent

superiority, of mibefradil in comparison with the long-acting nifedapine, and with amlodipine there was not a difference.

So, I guess the word "consistently" is the important one here. There's a suggestion that perhaps it might have some greater efficacy than other drugs, but certainly no consistent evidence.

DR. MASSIE: Ray, is this enough information on these points?

DR. LIPICKY: Yes.

DR. MASSIE: You don't want us to vote on any of these particular issues. Okay.

Let's move on to angina then. Does mibefradil decrease ischemia and increase exercise tolerance in patients with chronic stable angina?

DR. DiMARCO: Yes. I think that if you look at the curves and you can look at figure 61 in the briefing booklet, there seems to be a clear increase in almost any of the parameters. I'm looking at persistent 1 millimeter ST segment depression at the dose of 50 milligrams which is increased at 100 milligrams, and there's no real benefit apparent at 150 milligrams. The studies listed there are K13000, BC14047. I can show Joan the numbers there, but as you can see there are eight studies looking at that

particular parameter, and at 50 and 100 there's a clear effect.

DR. MASSIE: So, those are the trials that convince you and are you saying that 50 milligrams is the smallest?

DR. DiMARCO: There's no convincing effect at 25.

DR. MASSIE: What is the largest useful dose? I think you said.

DR. DiMARCO: There seems to be no benefit at 150.

DR. MASSIE: So, 100.

And you were choosing this what? Because there was no greater effects?

DR. DiMARCO: Yes.

DR. GRINES: Barry, can I make a comment on this?

I agree that all the studies consistently have shown an increase in exercise duration and the ST segment depression, but I guess I have a question for the FDA on what they call clinical improvement because if you look at what the clinician typically observes, which is the rate of anginal attacks per week and the rate of nitro consumption per week, I think it's very inconsistent. In fact, at 50

milligrams, only two of five studies showed a decrease in angina and only one of five studies showed a decrease in the nitro use. So, how do we resolve those discrepancies?

DR. MASSIE: Well, I think I heard the comment that a substantial number of those patients did not have anginal or nitroglycerin use.

DR. DiMARCO: At baseline.

DR. MASSIE: At baseline.

DR. GRINES: Why are they in the study?

DR. MASSIE: Because they exercise limited by angina. Is that not the case?

DR. TEMPLE: This has been a problem for probably 15 years. All the good angina patients have surgery, so they're gone.

(Laughter.)

DR. TEMPLE: And what's left is people who at the end of climbing 10 flights have a little chest pain. So, this has been discussed at workshops and guidelines and so on. We have long accepted -- that could change of course -- the idea that exercise testing with both ischemic and pain endpoints are a valid measure of whether something is antianginal and anti-ischemic. Typically there are too few attacks per week or too little nitroglycerin to have any reliable effect on those endpoints, although you do see

them sometimes.

DR. MASSIE: In particular, these placebo-controlled trials. I guess people who are using nitroglycerin regularly or having angina regularly are hard to enroll in a trial where they get no therapy.

The last part of 2 is, has mibefradil been shown to be consistently more effective than alternative therapy?

DR. DiMARCO: I think that it has been compared to other drugs. The drugs haven't been used at the maximum tolerated dose -- of those drugs, but they're drugs that have been used. So, I would say that it is not clearly superior, but it has an effect similar to.

DR. MASSIE: So, no.

DR. DiMARCO: No.

DR. MASSIE: It's not consistently better.

Okay, I guess we can move on.

DR. KONSTAM: Well, there's only one trial. Right? It's just the amlodipine comparison that shows that it's --

DR. DiMARCO: There's a diltiazem too.

DR. KOBRIN: The diltiazem study, the effect was similar and versus amlodipine it was a larger effect on all exercise test parameters.

DR. MASSIE: I must admit in my two years here, I've never had such an easy time defining the lowest effective dose and the highest dose. We usually spend an hour on that.

Are there mibefradil-associated repolarization changes in human electrocardiograms? John?

DR. DiMARCO: Gee, didn't we talk about that for a while?

(Laughter.)

DR. DiMARCO: I'll say yes.

DR. MASSIE: Too bad. We can't skip the next three questions.

Some electrocardiographic changes are ominous, but others are harmless anomalies. Do the available data, including the morphology of the observed changes, the results of electrophysiologic bench studies, the results of studies in whole animals, and the incidences of adverse events in clinical trials of mibefradil and other drugs, allow you to conclude that mibefradil-associated repolarization changes must be harmless and that their occurrence is therefore of no concern, regardless of dose?

DR. DiMARCO: I think that if you take the key word "must," no, they do not convince of that. I think the sponsor's have presented data and some very interesting

experimental data showing that these electrocardiographic changes are probably due to a different mechanism than similar electrocardiographic changes which are associated with proarrhythmia.

The clinical database for angina and hypertension has a very low incidence of events. However, as has been mentioned by other members of the panel, that was a group of patients who were carefully screened for presumably no symptomatic congestive heart failure, antiarrhythmic drugs were, for the most part, excluded, other drugs which prolonged QT interval. So, I don't think we can say anything about patients who have any of those factors.

I actually feel that data from the congestive heart failure study will be helpful in saying whether or not these phenomena are a potential harm, even though we won't know exactly the mechanism in those, and there are so few patients in higher doses, 150 or 200, I don't think we can say anything. I think we can say that the incidence of serious events in a very carefully defined population at 50 and 100 in the hypertension and angina studies was low. The pilot data from the CHF trial I think is very hard to interpret.

DR. LIPICKY: But, John, you didn't need to

answer the rest of the seven questions. This one only needed a yes or no answer and then you go on to the others.

(Laughter.)

DR. MASSIE: Is it fair to say that the word "must" must remain in the question?

DR. LIPICKY: Yes.

DR. DiMARCO: Okay. "Must" is an absolute term, and you can never say must.

DR. TEMPLE: Can I ask a question about something you did say, though?

The association of torsades type arrhythmias is not so clearly associated with other abnormalities as some other kinds of arrhythmias. Most of the cases, for example, on the antihistamines are not in people who are in sick. They're in regular, old, just ordinary people. That's one of the striking things you notice.

So, in that light -- maybe you're going to discuss that more later, and if it's premature, tell me if that's so -- how critical is the fact that probably these people didn't have heart failure to the question of whether it's likely to cause torsades? If you want to defer that, please do.

DR. DiMARCO: I think in a population defined as a group that doesn't have heart failure and doesn't have

antiarrhythmic drugs and doesn't have exposure to the drugs that the sponsor is going to recommend again, the data are there are almost no deaths and very few episodes of syncope. So, I think that that's very reassuring.

DR. MASSIE: Is there anybody on the committee who would want to further discuss the answer to that question? Does everybody want to say that they're totally convinced that there is no harm from this?

DR. KONSTAM: Well, I'd like to comment. It always boils down to a statistical question. The "must" is never 100 percent. To me I'm pretty darned convinced, enough that I would stop worrying about it.

DR. MASSIE: Well, wait, if that's what you're going to say, but you're not going to say "must," then we ought to go on to the next question.

DR. KONSTAM: No, I don't think that's fair.

DR. MASSIE: No. The next questions deal with those other types of concerns.

DR. KONSTAM: But you can never answer a "must" question yes. Never. That's why I don't think it's fair.

DR. MASSIE: Well, I think Ray's intent in these questions is if we say no, then we have to discuss this further, but we don't need to discuss it further at this instant.

DR. MOYE: Can I just follow up for a second?

When your response was that you're satisfied about this, let me just ask you --

DR. MASSIE: I do want to delay this discussion till where it's specifically relevant to the questions. This is the next series of questions I think.

So, we are not relieved of our responsibility to move on to the additional questions.

DR. KONSTAM: Barry, I'm sorry. Let me just clarify my position about this.

I'm convinced that we don't have to worry about this anymore. I don't know how much closer to "must" you can get.

The reason I'm convinced of that -- and I actually look to John DiMarco to really tell me that this logic is wrong -- is that we have a signal, an abnormality on a surface ECG, which is a very rough thing. I've been pretty reassured by some electrophysiologic experts that in every single case where a drug has been associated with torsades and an abnormal repolarization on ECG, that it's association with prolongation of the action potential duration, drug after drug after drug.

This is a drug that electrophysiologically is very different and we have an alternative explanation for

the surface ECG. I'm satisfied that the signal misled us.

It's sort of like you spot a van with fertilizer and fuel oil.

(Laughter.)

DR. KONSTAM: And you worry about it a lot and you send out the FBI because that's appropriate. And then you investigate the guy the best you can, and it turns out, well, he's a farmer and he's been doing this for a long time. How much further do you investigate it? Are you absolutely sure that he's not intending to blow something up? I think you're pretty darned sure when you know that he's been doing it for a while.

This is I think an analogy. I think the surface ECG led us to something. It was investigated. We have some very good alternative explanations for it. I'm satisfied with that.

DR. MASSIE: Okay. Let's move on.

At what doses of mibefradil do repolarization changes occur? Are these doses so much higher than the therapeutically effective doses that repolarization changes are of no concern? I don't think that means in terms of outcome, but that they don't occur at a dose that it would be used.

DR. DiMARCO: Well, I think we've heard from

the sponsor that they're seen in 4 percent of people at the 100 milligram dose. So, the answer to that is they do increase at higher doses, but we are seeing them in a significant proportion of the patients at the highest dose they're recommending.

DR. MASSIE: What? Yes, the answer is no.

Is it reassuring to compare the mibefradil-associated repolarization changes to those seen with other drugs? In particular, can you conclude that mibefradil-associated repolarization changes are no different from those that are seen with other drugs that are known not to induce malignant ventricular arrhythmias?

Now, wait. Too many negatives there.

DR. DiMARCO: There are too many negatives, yes.

DR. MASSIE: Let's try that again and make sure at least that John understands the question.

Can you conclude that mibefradil-associated repolarization changes are no different than those seen with other drugs that are known not to induce malignant ventricular arrhythmias?

(Laughter.)

DR. LIPICKY: Maybe I think the question is, since it looks like verapamil and diltiazem, does that make

you feel good?

DR. DiMARCO: The changes do look like verapamil and diltiazem, and it makes me feel better.

DR. LIPICKY: But not good? You're still sick?

(Laughter.)

DR. DiMARCO: Pretty good.

DR. MASSIE: Let's move on to the next subpart, 6(A)(1). At what doses of those drugs, verapamil and diltiazem, are these repolarization changes seen?

DR. DiMARCO: Well, I think again they were shown at doses of verapamil of 480 milligrams and 960. I don't think that they've scanned all verapamil patients treated with lower doses, so we don't know when they might start to pick up a 4 percent incidence. So, my guess is that it's roughly in the same realm of relative doses as those two drugs.

DR. MASSIE: Okay, so then they're seen in doses -- high doses of -- the upper end of the therapeutic range, we think they're still seen and with the verapamil and diltiazem.

DR. LIPICKY: Is that really a fair impression to leave? I mean, that's not the high end of the verapamil dose that's beyond the high end of the verapamil dose.

DR. MASSIE: Isn't 480 the highest approved

dose?

DR. KOBRIN: 480 verapamil and also 360 diltiazem.

DR. MASSIE: At least 360 is certainly not even the highest approved dose.

DR. LIPICKY: Okay.

DR. MASSIE: I think.

So, we can move on to 6(A)(2). Are those other drug doses so close to the therapeutic doses and are those drugs known to be so safe at therapeutic doses that the mibefradil-associated repolarization changes are no longer of concern?

DR. DiMARCO: I can't really speak to the entire diltiazem and verapamil databases, but general impression is that those drugs are not associated with polymorphic ventricular tachycardia.

DR. MASSIE: So, you're concluding because of the similarity to these drugs, that these are not of concern. That's the second part of the question.

DR. DiMARCO: Yes. I'll say yes.

DR. MASSIE: Anybody else have any discussion on that point?

DR. LIPICKY: Can I just clarify one thing?

The study that looked at verapamil and

diltiazem was how many subjects?

DR. KOBRIN: In the verapamil, there were two studies. Each one was 6 subjects, and the diltiazem was 6 subjects.

DR. LIPICKY: So, your conclusions are being based on 18 subjects. I just want you to recognize that. You can conclude exactly as you're concluding if you wish.

DR. DiMARCO: The conclusion is that the changes on the ECG can be produced at doses that are similar. The safety conclusion would be based on a general experience with those drugs. That's why I hesitated a little bit. We don't know whether these repolarization abnormalities -- what significance they have, but it appears that if they are of ominous significance, it's the same for verapamil and diltiazem which have not been associated clinically or at least in data that I've seen with a higher incidence of malignant arrhythmias.

DR. TEMPLE: Parts A and B are two parts of a question about how one gave the assurance. The first was if verapamil does the same thing, does that reassure you because you're pretty sure that doesn't cause torsades. And then the second one is about the distinction between the electrocardiographic findings with mibefradil and the electrocardiographic findings with drugs that are known to

cause problems.

So, I guess if the verapamil/diltiazem data were standalone overwhelming, this is all now put to rest. The right answer to that is yes. If it's close to that but not quite, give us some indication of how strong it is. I think otherwise we won't have your full views.

DR. MASSIE: I guess the thing is you said that together with other information. So, if that alone is not totally reassuring, we go on to 6(B).

DR. DiMARCO: I think this is a new phenomenon that we haven't described for verapamil and diltiazem before, and I don't think anyone can say that no one knows that this phenomenon doesn't have some significance. It's just that when verapamil and diltiazem have been looked at, it has never been detected above some threshold level, but we really haven't reviewed large databases with those drugs today.

So, I think this is a phenomenon seen with drugs that are in common use that are not commonly associated with or not thought to be associated with malignant ventricular arrhythmias. The phenomenon with this drug appears to be the same. The exact significance of this phenomenon is still unknown, but it has got to be of limited significance or of the same as those drugs which

we haven't looked at this closely.

DR. LIPICKY: Can I ask you what you think the same is? It's some change in the S-P but in fact the ones I looked at didn't quite look like the changes that occurred with mibefradil. It certainly changed the T-wave and what happens after the T-wave, but it didn't quite look exactly like the same thing. This is in spite of what Dr. Pratt's study says.

DR. DiMARCO: I must admit I didn't have enough to look at all of them, and obviously you looked at 38 of the patients from the mibefradil. But I find T-waves and these U-waves so difficult and so changing over time that I can't say that there is one single pattern that is very characteristic. They all look to me to be in the same family.

DR. LIPICKY: Something in the S-P.

DR. DiMARCO: Well, but there's also an emergence of a U-wave. Now, Dr. Noble says that he thinks this is the U-wave that was buried before. An alternative explanation would be it's an appearance of a U-wave that wasn't there as the T-wave shifts. So, I don't think we can say that for sure.

DR. CALIFF: I just want to voice a concern about so much fixation on these little, what we call

microcardiology changes on the ECG. We know there are drugs that prolong the QT interval that are associated with good health effects and drugs that prolong the QT interval that are associated with bad health effects. We don't know by looking at the EKG how to tell one from another, and now we're talking about dissecting the EKG even further and drawing conclusions from it. It seems like we need to go to the safety database and draw our conclusions.

DR. MASSIE: Well, I think that's where we're heading.

Bob.

DR. PRATT: You can believe it or not, but the company has made arguments that you can tell something about what the significance of the electrocardiographic finding is from looking at animal studies and in vitro studies and stuff. Now, maybe you consider that part of the safety database, but there are other things one could look at. Whether they're persuasive or not is another question.

DR. MASSIE: I wanted to ask Ray, since you have, of the people at this table, the greatest experience with looking at these ECGs, what was different in your opinion between the changes that you observed with mibefradil and verapamil?

DR. LIPICKY: Well, it's very hard to describe that. The place where you really couldn't tell a U-wave anymore wasn't there. You could see two humps, but you never only saw one hump, and that kind of stuff. I must admit I didn't try to systematically sit down and say what the similarities and dissimilarities were. I'm not sure. That's why I asked. I'm not sure that it's the same cow, but I'm not sure that it might not be a Guernsey or something.

DR. MASSIE: Craig?

DR. PRATT: We had this very small, admittedly very small, study but we did try to do something objective. Everything here we're seeing is subjective. We asked people to give their subjective opinion blinded to which of these three drugs it was, and three experts couldn't tell a difference.

I'd just like to read one of the things that Dr. Waldo has to say about a verapamil ECG. He wrote this. Of course, he did not know what the treatment was. "Importantly, I think the only thing of potential interest and perhaps meaning is the apparent change in comparing baseline on therapy in the shape of T and U and Q-T-U. In all cases, it became really hard to know where the T ended and the U began, and the shape of the T-U complex was

unusual." He's talking about a verapamil ECG. It sounds like the entire thing.

I think these are all overlapping issues.

DR. MASSIE: Well, I think we can probably move on to 6(B). That is to say, we're not sure that they're not -- well, John thinks they're about the same and that's reassuring I guess it's fair to say.

Can you conclude that the mibefradil-associated repolarization changes are different from those seen with other drugs that are known to induce ventricular arrhythmias?

DR. DiMARCO: Looking at it two ways, I think the preclinical profile is certainly different than the vast majority of drugs. The ECG -- I don't think I could tell the difference between the changes that are seen here and some changes I've seen with drugs that are associated with torsades. So, I don't think the ECG helps me make a distinction.

DR. LINDENFELD: I'm just interested in sort of a rough estimation of what size database it would take to see a change in torsades. What did it take with bepridil? What do we need to see that?

DR. KOBRIN: To see what?

DR. LINDENFELD: To see if there is an

increased incidence of malignant arrhythmias. In other words, we have a database for which there are some concerns in the heart failure, that small group, but what size population did it take to see the incidence, for instance, in bepridil? How many patients treated?

DR. KOBRIN: I think that in order to eliminate an incidence of 1 in 1,000 or less, you have to go to tens of thousands of patients in order to be able to rule it out, and that's the case for any NDA.

DR. MASSIE: Craig, I know you've looked at this with other drugs. Is that your feeling?

DR. PRATT: Yes. I'd like to go back to something Dr. Califf said. I think it's very important. I think the committee is discussing a different concern, and we have torsades brain. It just seems to come over and over again.

Ray's point about MACH 1, even if we knew today every death and the ascription of cause of death, it wouldn't help him answer whether or not there's an occasional patient with torsades. It's only looking at the entire preclinical database and everything else, you're either convinced that torsades is likely to be here with this drug or it's not and nothing is going to help that 1 in 1,000 likelihood.

I think the other issue is the issue of how this drug fares in terms of overall mortality, not cause-specific mortality, and that's I think what Dr. Califf was describing. It's a different question. I think we've kind of drifted back and forth between those two questions all day.

DR. MASSIE: Your first point, that you have to look at the entire database and decide whether or not torsades is likely to be there or not. You've looked at other databases, and would you have concluded that torsades that is not likely to be there with terfenadine?

DR. PRATT: Terfenadine?

DR. MASSIE: Yes.

DR. PRATT: Well, you see, to contrast it, since I've published on it --

DR. MASSIE: That's why I'm asking.

DR. PRATT: -- I think that you have in that situation a very different preclinical situation and you have a dose proportional change in QT. And like other drugs that cause a dose proportional increase in QTc, there are in some cases the possibility of torsades. With that drug probably only, at least based on things that we've done -- in fact, Dr. Moye and I collaborated on -- in the presence of things like ketaconazole, erythromycin, et

cetera. But it is related to that dose proportional change in QTc, and I think it is a signal that means something.

I think here we have a totally different signal which we're trying to ferret out whether this is a red flag or a red herring.

DR. LIPICKY: Craig, six months ago or really two weeks ago I would have believed your statement 100 percent, but now having looked at these electrocardiograms, I don't believe anybody that tells me there is a QTc change because I never read U-waves before either. And how would you assure me that in fact you knew what you were doing when you were measuring the QTc?

DR. PRATT: Well, I suppose one thing we could do is we did have the database upon which -- in fact, Dr. Moye and I even described the variability of QTc, interpatient and group variability. We could go back and look at all those ECGs and make sure that we were not blind and didn't miss U-waves in every patient. It's my belief that we didn't, but I must say I haven't reviewed it lately, like for three or four years. And that database would still be available and I don't think it's an unreasonable thing to do. I would be willing to do it.

DR. MOYE: Of course, the difficulty here is that the incidence rate of torsades is so small that it's

almost beyond the resolving power of clinical experiments to capture it reliably. When we tried to design prospective controlled clinical trials, you need not thousands, but hundreds of thousands of patients all for a great period of time in order to be able to pick up a reliable treatment effect on torsades.

If you then turn to retrospective studies, like historical cohort studies, you can use available databases, but of course the methodology introduces biases such as bias by therapeutic indication which increases the noise and makes it very difficult to pick up the signal. So, every step out of a problem is a step into another one, and it all has to do fundamentally with the extremely low event rate of interest.

DR. LIPICKY: Barry, can I say one thing? I don't know if this will help either.

It is not unusual for us in the case of approval of an antihypertensive or approval of an antianginal to accept lowering of blood pressure as the basis for approval and an increase in exercise tolerance as the basis for approval, as long as it's also anti-ischemic.

We recognize that an NDA database that may be up to 3,000 or 4,000 patients is a very small database, such as this one. There aren't very many bad things that

happen to patients in that database. We don't expect to be able to make judgments about morbidity/mortality from that NDA database.

Therefore, we're fairly careful about looking for what Craig said, dose-related increases in QTc. That was something that was part of the way in which this data was reported originally.

As it turns out, it may well have been a dose-related something, but I haven't heard anyone say that that dose-related something is not the same as a dose-related change in QTc. Because I haven't heard anyone say that the databases that they used to say was a dose-related change in QTc, they're sure of really that fact and not this.

DR. KONSTAM: You know, I guess you have to get back to asking the question why are we concerned about dose-related changes on the surface ECG at all. I guess it comes from the fact that there are drugs that are known to cause torsades that are associated with repolarization abnormalities on the surface ECG. You have to look at the totality of the data and ask yourself is that what we have here. Personally I'm convinced that it isn't.

The principal thing that convinces me of that is that the basic electrophysiologic mechanisms in play in this drug are very different from all of the other drugs --

and somebody stop me if I'm wrong -- but all of the other drugs that have caused torsades.

DR. LIPICKY: This is APD now you're talking about?

DR. KONSTAM: That's right.

DR. LIPICKY: APD.

DR. KONSTAM: That's right.

DR. LIPICKY: So, the APD is the thing that makes up your mind.

DR. KONSTAM: That's right. And I really look to John particularly to tell me if I'm going astray here, but I'm pretty convinced by that.

DR. DiMARCO: Keep going, Marv.

(Laughter.)

DR. KONSTAM: I'm pretty convinced that that's the key, and that the surface ECG is spotting something that is linked to prolongation of the APD, and that's not what we have here. Therefore, yes, there's something on the surface ECG, but I don't have any reason to worry about it.

DR. MASSIE: Well, maybe we can focus on 6(B)(1) and 6(B)(2), which I guess are the times where John gets to tell us whether or not he feels -- first off, what are the mibefradil-associated data that would convince you

that this is so, that is, that this is different from other drugs known to cause malignant ventricular arrhythmias?

DR. DiMARCO: I think what allows me to feel fairly confident about this is the basic data that have been presented by the sponsor showing that the changes are different. I was very intrigued by Dr. Noble's presentation about the mechanism. I think that will probably require confirmation, but it does provide a rational explanation for this.

Again, I don't think that you can tell much from the surface cardiogram, so I am basing this mostly on the basic science profile of the drug which is well characterized and which can be used to explain the ECG changes.

DR. MASSIE: And are there other drug-associated data that convince you this is so? Is this back to the other calcium blockers I guess or other information about other malignant arrhythmias?

DR. DiMARCO: It is reassuring that one of the tests of the hypothesis that this is due to action potential shortening is two other drugs that produce the same effect, produce the same ECG changes.

DR. MASSIE: Ray, do you want us to vote on any of these questions?

DR. LIPICKY: No.

DR. MASSIE: Does anybody want to espouse a different opinion than John on his degree of reassurance? Bob?

DR. TEMPLE: You've heard this before, but I need to get your view.

My inclination is to ask for some analysis of electrocardiograms for showing QT prolongation for drugs that we do know cause a problem, terfenadine or astemizole and things like that, to take a look and see whether on close examination by Dr. Lipicky he could resolve them into the same kinds of non-QT prolongation that he did with the samples here.

Now, do you think that's unnecessary, stupid, a good idea, or what?

DR. DiMARCO: Well, I think it's one of those situations where if you got a change that was different, you'd feel reassured, but not positive. But I'm not sure you'd get a change that was different. I think the variability in these cardiograms is so great that these are very difficult measurements to make. So, even if you got the same thing, that wouldn't worry me more. I don't think that that's going to help me either way.

DR. TEMPLE: Let me be clear on that. The

company spent a lot of time showing the phenomenalism of QT prolongation was not in fact QT prolongation but U-wave and T-wave modification, which was certainly news to everyone and not known initially.

If I understood what you just said, you're saying even if what terfenadine does is exactly that, some other information -- I presume the animal data and various models -- are reassuring enough so that you wouldn't even care.

DR. DiMARCO: What I'm saying is it would not surprise me that a competent observer could look at terfenadine and get the same result Dr. Lipicky got.

DR. TEMPLE: So, the so-called QT prolongation could just turn out to be a complete fiction, something that doesn't actually happen at all, as it doesn't happen here.

DR. DiMARCO: I think that it's very hard to make those measurements. Exactly what the QT interval is and how it relates to the U-wave, what notch is really important, how to make that calculation down of the down slope like Ray was looking at the peak and he was looking at the notch, how do you extrapolate that down, they're all uncertainties, and whatever you find is going to be based on what your assumptions are. And yet, I don't know if

there are good relationships there.

DR. TEMPLE: Well, for sure, not every case will be resolvable, but Ray couldn't find any case where he thought there was documented QT prolongation among that group of electrocardiograms where someone thought there was. I guess I would have thought that unless we're completely wrong about the phenomenon, at least with some of those other cases you'll be able to say, well, I don't see a U-wave here. This looks real. But you're not so sure about that.

DR. DiMARCO: I'm not so sure, but I can't say for certain.

DR. TEMPLE: So, it would help if you could learn that, if you saw, oh, well, this looks different.

DR. DiMARCO: What would you do if you had 50/50?

DR. TEMPLE: I would then be reassured considerably actually because I would then know that where QT prolongation is linked to disaster, you often at least can see actual prolongation of the QT, whereas here there wasn't any of that. Not one case withstood Ray's scrutiny.

DR. DiMARCO: If you took that absolute thing, then it might be helpful because I was basing my thing that I think that you'll find situations for terfenadine where

the QT is long and which by Ray's criteria it would actually not --

DR. TEMPLE: Yes, I'm sure of that. There would be some where there would.

DR. DiMARCO: Yes. My guess is there will be, yes.

DR. LIPICKY: But then if I sum up the discussion as it is now, what one can do is stop measuring the QT and simply measure action potential duration in guinea pig atrium, and if that shortens, you don't care what you see on the cardiogram. That's what you've just said.

DR. CALIFF: I've had a standing dinner for two available to any house officer who can give me empirical data to show that it's useful to measure the QT in patients. So, you may be right. It's interesting, fun to look at, but --

DR. MASSIE: Well, if you've got a bet --

DR. CALIFF: Twelve years.

DR. LIPICKY: What is the bet?

(Laughter.)

DR. CALIFF: If you're looking for a dinner, you'd have to come to Durham.

(Laughter.)

DR. RUSKIN: I think the question of what to do with the long QT interval is a hard one to answer. Again, this is clinical anecdote. I don't have an extensive database, but there's no question that drugs like quinidine or sotalol which are known to cause torsades and known to prolong the QT interval will in some patients make the measurable QT interval longer when you can see a U-wave both before and after. The QT interval will get longer in some of those patients.

What I can't exclude with certainty because I don't have the data is whether or not there are some patients in whom T-U fusion may occur, such as Ray has described, and may be part of what you see with those drugs.

But I think it's important to point out that when you can measure the QT interval and when you can see the U-wave before and after, the QT interval will get longer with drugs like quinidine and sotalol and amiodarone.

DR. MASSIE: So, it would be your hypothesis, if we did what Bob suggests and give Ray some more work that includes some ECGs with other drugs that we know cause torsades, that he will be able to distinguish a difference.

DR. RUSKIN: I think you'll see differences.

What I can't say, because I don't have the data and I've never studied it in a systematic way, is what the percentages will be and how many might fit into this gray zone.

DR. LIPICKY: Can I just say one thing? This is not my fault. This is not my discovery.

(Laughter.)

DR. LIPICKY: All I did was read some ECGs. The company found this. Isaac is the one that described this phenomenon.

DR. TOMASELLI: Again, this is my impression of things here, but I think we're trying to infer a mechanism from what is truly body surface electrocardiographic phenomenology. I think what the company has shown is that you could probably produce things that look similar on the body surface both from prolongation and from reduction in action potential duration.

The mechanistic link that we who study cellular events believe is it's the action potential prolongation and associated phenomena like after depolarizations that are really coupled to torsades de pointes and polymorphic VT. And that's the critical issue as I see it.

The other thing is this is not a static phenomenon and there are other things that people who have

long QT intervals who are going to get torsades on quinidine or on other drugs have, like persistent bigeminy, like very large variability in the beat-to-beat behavior of the QT interval.

So, I think the bottom line is trying to infer mechanism from body surface electrocardiographic phenomenology I think is very difficult.

DR. MASSIE: Well, I think you're right but I think that Ray asked a provocative question which I personally would respond that I'm not willing to decide electrophysiologic risk or no risk from measuring action potential duration in guinea pigs or computer models. Clearly what we want is a safety database, but short of having the most extensive safety database, it would be reassuring to have some feeling that there are differences on the body surface ECG between dangerous drugs and un-dangerous drugs.

DR. TOMASELLI: I agree the safety database is the ultimate bottom line, but I think it's difficult to infer too much from what happens on the body surface electrocardiogram just in terms of risk.

DR. MASSIE: Well, we're at the end of question 6. Ray says no vote.

I'd like to hear from other panel members

whether we want to keep Ray employed reading ECGs or not. Does anybody think it's worth doing this? Obviously, John is quite ambivalent about its utility.

DR. KONSTAM: I wouldn't do it on the grounds that I think you could make Bob feel better, but I don't think that there would be anything that could come out of it, speaking for myself, that would convince me that there's a problem. In that light, personally I wouldn't do it.

DR. MASSIE: Anybody else?

DR. TEMPLE: Making me feel better is not a trivial thing.

(Laughter.)

DR. TEMPLE: I have to sign this thing, you know. Feeling better is good.

DR. MASSIE: I think we need to move on.

Besides the effect on repolarization, does mibefradil have other electrophysiologic effects on the heart? If so, what are these effects and at what doses do they occur?

DR. DiMARCO: I think we saw effects on particularly the AV node and the sinus node similar to those seen with other calcium channel blockers. They are dose-related. They increase, but they're detectable during

the dosage intervals that the manufacture is talking about.

DR. MASSIE: Are you concerned about those?

DR. DiMARCO: No.

DR. MASSIE: Are there other safety concerns pertinent to the approval of mibefradil? Mike, do you have any others?

DR. WEBER: No. The only issue that has been raised -- so I won't go into it again -- were the deaths in the early pilot work and the CHF protocol. Other than that, I did not see anything that would make this drug give me any more concern than other calcium channel blockers or other antihypertensive drugs.

DR. MASSIE: John?

DR. DiMARCO: My only safety concern is, since this is a relatively new phenomenon, I don't really know if we combine this with other drugs that affect repolarization, either by the same or particularly by different mechanisms, whether that has any ominous significance. Those patients were for the most part excluded from these trials. So, I think it's an unanswerable question on the basis of these data.

DR. MASSIE: Do you think it should be so indicated in the labeling that there may or may not be some risk?

DR. DiMARCO: At the present time, I think that labeling should say that this phenomenon in the Q-T-U or QTc, as it probably will be measured by most people, has been noted, and the interaction with drugs which are known to prolong the QT interval and produce arrhythmias is uncharacterized, and I would not use this drug in those patients until there has been more experience.

DR. MOYE: I'd like to follow up on that. I'm still concerned about the need to reassure both the national community of physicians and the public at large. I have heard and am respectful of and learned a great deal about electrophysiology this morning, but I think the best reassurance for the public is not theory, it's data.

Having said that, I recognize that I am boxed nicely into a corner because, as Craig has appropriately reminded me, the DSMB would probably not allow for early unblinding, and Ray has appropriately reminded me that even if they did, incidence rates from one population are not necessarily predictive of incidence rates in another population. And I remind myself that we can't have a de novo trial looking at this issue in the population of interest because it would be much too large and probably impractical to carry out.

So, I can't have the trial I want, so I must be

able to use the available data. And if I can't do that, then I have to use data when it becomes available, and to me that means that the best -- not very attractive to be sure -- but the best thing, the best option before us I think is to wait until we have some information from the heart failure trial.

I'm afraid that we are rushing into this. This is a new mechanism. We have heard from the learned experts that they must speak, despite their experience, from their own clinical experience and with anecdotes because they don't have the data set that we need. We are likely to never get the data set that we would like. So, I'm just asking that we be patient until we have some more data that allows us to address in some sense the incidence rate of sequelae from this new phenomenon.

DR. MASSIE: Marvin?

DR. KONSTAM: Yes. I pretty much agree with the position that Craig stated -- and Rob and others have said some similar things -- that there are two separate issues. One is the ECG which personally I'm not worried about. The other is this signal emerging from the heart failure database that I am concerned about.

One of the reason that I'm concerned about it is that it fits some other stuff that we know about calcium

blockers in patients with heart failure and ventricular systolic dysfunction, and I think putting those two things together and that similar data signal, outcome signal, does not emerge from the hypertension and angina population per se that excluded patients with heart failure.

Personally I'm concerned enough about that signal that I would put some kind of a caution or deal with that in some way in the population of patients with reduced systolic function until the MACH 1 data are available. I see nothing in the data that keeps me away from the hypertension and angina population as long as they have normal systolic function, but I think we need to deal with that latter population somehow.

DR. MASSIE: Let me just ask, isn't there some sort of general caution in all the calcium blockers?

DR. LIPICKY: Well, I can't swear to it, but there should be. It ought to say calcium channel blockers aren't good for people whose ventricles aren't working well.

DR. MASSIE: I'm pretty sure there is.

DR. TEMPLE: Well, Barry, there is.

DR. MASSIE: -- just got removed with amlodipine as a result of --

DR. LIPICKY: Well, that was sort of one of

those deals.

DR. KONSTAM: Can I just raise another point about that with regard to -- let's say, assuming the MACH 1 when they came out were neutral or even positive. That would still not completely take my concern away, and it's for this reason.

There's a difference between the MACH 1 study and the other studies, and one important regard is that all the MACH 1 patients are on ACE inhibitors. I think it's entirely possible that the adverse effect that may be present in calcium channel blockers in patients with low systolic function, that the difference that we've seen in different trials in the past is not so much related to differences in drugs, but related to differences in background therapy. So, the MACH 1 data will have a patient group that is very different in terms of background therapy than the database that we're looking at in hypertension and angina. So, I'm not going to be completely persuaded from the MACH 1 data that the drug is safe in patients with low systolic function.

DR. CALIFF: It's painful to say this because this has been a great presentation and the data have been presented very clearly. But I think Lem has a critical issue, and I pretty much agree with him. The term has been

used "population of interest." People with hypertension and angina are not, by and large, people who have no other diseases and are feeling pretty well. It's a mixture, a very heterogenous population.

I think it's concerning that the mortality data look the way they do right now, but not definitive. My hunch is that things are going to be fine and the company has done the right things all the way along. So, it's not a critique of the way the problem is being approached. It's just that it's hard to say that there are no safety concerns at this point. My hunch is that everything will be fine when the data come in, but with the imbalance that we currently see in the data that's available, the degree of doubt is significant, at least on my part.

DR. MASSIE: Mike?

DR. WEBER: I think what you're saying, Rob, is basically correct, but as someone who spends a lot of time dealing with hypertension, issues of occult or unknown left ventricular systolic dysfunction occur surprisingly infrequently. They do occur, no question about it, but in a very small proportion of patients. It would be very hard for me to recollect from my own experience ever being surprised or upset that someone I have put, say, on a calcium channel blocker has suddenly developed any

problems.

I wonder if I could get Suzanne Oparil, who's here and is very knowledgeable in these areas of clinical hypertension, to make a comment on that, whether I'm being too easily satisfied on that.

DR. OPARIL: Yes. From the clinician's point of view, many patients do have comorbid conditions, left ventricular hypertrophy, even overt failure. Usually the big hemodynamic problem is high after-load if their hypertension is uncontrolled, and lowering blood pressure usually makes them better, not worse, even if the agent may have some intrinsic negative inotropic effect.

DR. MASSIE: Let me just raise one question. We have at least one calcium blocker, I think diltiazem, that had a post-infarction study where the group of people that had LV dysfunction did worse, and that was not an angina population but probably not too distinguishable from an angina population.

The question is what do you do with that information. Let's say MACH 1 comes out that way. What do you do with your angina and hypertension claim? I'd guess I'd ask Rob that.

DR. CALIFF: It would depend on how substantial the difference was. In the absence of seeing the

information, it's just hard because I imagine a circumstance where if there was a negative effect, it would be small enough that it wouldn't bother me to be part of letting the drug out on the market for people without LV dysfunction. Yes, there could be such a small effect that would still be significant, but I can't say exactly what it would be.

DR. TEMPLE: All calcium channel blockers, until they do a study showing otherwise, bear some warning against use in people with heart failure. I think it says heart failure, not LV dysfunction. Maybe that's a defect.

We need to understand the implications of what you're saying which I take to be that a drug should not be approved for angina or hypertension because some of those people have LV dysfunction until you carry out a study in overt heart failure.

There are a lot of things that have come up today that I think may need some sort of workshop approach because we shouldn't move lightly to requiring many-thousand-patient trials without a clear indication of what we're about.

But is that what you're saying, Rob? Because that is clearly a new standard for approval of angina drugs.

DR. CALIFF: I'm going to stake out that extreme position at this point because to me we treat hypertension to reduce the risk of stroke and death and renal failure. I can think of a lot of ways I could lower the blood pressure and kill people, and when we treat angina, I think you said it very well, there are not many people who are disabled by severe angina today because people get revascularized and we have many other effective treatments.

So, when we treat angina, we're really treating ischemic heart disease, and to promote the use of a therapy because it makes people's symptoms better without understanding the other side of the coin, what it does in terms of the major issues that concern us in the treatment of ischemic heart disease today, seems to me to be treacherous at the least in terms of the public health.

Now, I would look at it differently if there was a wonderful up-side that was not available. If this was really something that was dramatically different, better than anything else in the way of relieving symptoms, then I would look at it differently. But given the fact there are a lot of other effective therapies out there, why not be safe with the public?

DR. TEMPLE: Well, a short answer is you don't

know the answer to the question you pose for an event.

DR. CALIFF: That's right.

DR. TEMPLE: There are no mortality studies in ordinary angina that I'm aware of.

DR. CALIFF: But just because you did things wrong in the past doesn't mean we should continue that. We've learned a lot.

DR. TEMPLE: I'm not necessarily taking the position. You can guess I'm nervous about this.

But the development of antianginal and antihypertensive drugs has had up to now databases of 1,500 to 2,000 people, but there has not been a requirement and not much thought going into what kind of mortality studies you do.

What's particularly important about what you're suggesting is that you're asking for a mortality study in something that isn't even a claim. There isn't, for the most part, with calcium channel blockers a desire to treat people with heart failure, and I think you're defining it as a needed safety study. We don't know what the size of those studies would be, but I would say conservatively they've got to be several thousand to be reassuring as a precondition to approving drugs for angina and hypertension. I'm just saying that's the sort of

requirement that one needs to think about at some length.

DR. CALIFF: Let me just say with regard to my last statement it was unfair. I think we've learned a lot in the last few years about the overall health effects of therapies. I think from my perspective it is time for a change in this particular field.

I can guarantee you that if you had a few thousand patients and put in the kinds of patients that are being treated in practice into the trials, you'd at least have a better estimate than the way things are currently done with these pristine patients who can't represents what's in practice, as you said, because anyone who had significant angina wouldn't go on placebo, for example.

DR. MASSIE: I think we're into the philosophical, although it obviously might affect some people's votes. However, we have 10 minutes and we have to vote on three more questions. So, unless somebody has something brand new to say -- do you have something brand new to say?

DR. KONSTAM: Well, I'd just like to disagree with Rob. I think it is --

DR. MASSIE: That's not brand new. You've been disagreeing on this point all the way through.

(Laughter.)

DR. KONSTAM: No. Actually I've agreed with just about everything else he said up till now, to tell you the truth, because I'm concerned about the same things he's concerned about.

But I think it's personally too extreme to keep the drug off the market because of the signal that we see in the heart failure population. I don't see what data come to bear on that particular argument. I think if there were something big going on, I'd expect to have seen it in the 3,000 population randomized on the hypertension/angina, and I don't see it.

DR. MASSIE: I must say that if we had our choice to have a survival or morbidity/mortality trial in the drugs we're looking at for hypertension and angina, I'd much rather see it in hypertension and angina than in heart failure, but maybe we should have both. But if we're going to do that, then we have reinvented the world.

But I think there was a committee meeting not too long ago that certainly tried to incentivize people to looking at morbidity and mortality in hypertension, and we're seeing more trials, and maybe even this product will be the subject of such a trial some day.

Let's move on to question 9. Should mibefradil be approved for the treatment of hypertension?

I'm not sure we need much further discussion. I think that's what we've been discussing.

I'm going to ask the two primary reviewers to vote first and then the rest of the committee. John, why don't you start?

DR. DiMARCO: I would recommend approval. I would recommend doses of 50 and 100 milligrams.

DR. MASSIE: Let's just do yes.

DR. DiMARCO: Okay. Yes.

DR. MASSIE: Mike?

DR. WEBER: Yes, exactly the same. I would support approval at the doses that we've discussed.

DR. MASSIE: Marv?

DR. KONSTAM: Yes, but I'd like to see some strong wording cautioning against use in patients with LV systolic dysfunction. Does that come in later? Whatever. It's a qualified yes.

DR. RAEHL: Yes, qualifications to follow.

DR. MASSIE: Lem?

DR. MOYE: No. I think it's premature. I think the sponsor should be lauded for this excellent and honest and frank workup of a very difficult, new problem, and I think that we have to do a little more work and be a little more patient. So, perhaps the drug is good, but

let's be sure.

DR. LINDENFELD: I would vote no for two reasons. Just what Lem has said and I'm still not totally convinced that the action potential duration is an adequate surrogate.

DR. MASSIE: I have to abstain.

DR. CALIFF: I vote no for the same reasons as Lem. I would be willing, if there was a way to get the interim results of the heart failure trial and it looked good, to reconsider very quickly.

DR. GRINES: I vote yes.

DR. MASSIE: 5 to 3, so we have to go on to 9(B).

Basically the question is, are the repolarization changes sufficiently worrisome that labeling should relegate mibefradil to second-line therapy for hypertension, that is, basically only to be used for patients who do not respond to other therapy?

I think that's an additional vote. I guess we'll start with John again.

DR. DiMARCO: I'll vote no. My concern is not about people responding to other drugs for hypertension. My concern has already been expressed about other drugs which have known arrhythmic potential.

DR. MASSIE: Mike?

DR. WEBER: Yes, I think this may be the last time we'll be talking specifically about hypertension, so I'll agree with John that I'm not worried anymore about repolarization. But I do agree with the point that Marvin has been making -- and I'll let him speak on it more lengthily -- that there should be clear labeling about left ventricular systolic dysfunction.

On general principles too, I don't agree that the drug should be indicated or used for second-line treatment. If it's not considered worthy of first-line treatment, frankly I don't see much point to an alternative.

I think it's a useful drug. I think it lowers blood pressure well. It lowers blood pressure I suspect better than most available drugs and slightly reduces the heart rate which is also useful for treating hypertension. So, I think it will be quite a useful addition and with the appropriate labeling caveats, I think it should be a first-line drug.

DR. MASSIE: Let's start down at this end. Cindy?

DR. GRINES: We're on 9(B)?

DR. MASSIE: Yes, 9(B). Yes would be it could

be a second-line drug; no, it is not.

DR. GRINES: No. I think first-line agent is okay as long as we put the warning about no knowledge of left ventricular dysfunction.

DR. TEMPLE: I just wanted to ask, we don't just count the votes. We try to listen to the words that people use too. So, I want to ask the three people who did not think approval should be supported a little bit about the reasons. I hear at least some concern about the possibility that the repolarization problem is still real. I understand that part.

I want to be sure I understand what the purpose of getting MACH 1 data would be, and I'll give you some choices. Is it to resolve the problem raised by the pilot study? That's number 1. Is it because it's necessary to characterize the effect of a calcium channel blocker on people with heart failure before you can put it out even for people who may not have heart failure but you need to know the answer as part of a proper workup of the drug? I guess those are my two.

DR. MASSIE: Let's finish this vote.

DR. TEMPLE: Oh, I'm sorry. I thought you had.

DR. MASSIE: We're still in the second-line therapy.

DR. TEMPLE: I'm sorry. I thought you had finished the vote.

DR. MASSIE: Then we'll come back to your question.

Rob?

DR. CALIFF: I would say it should be second-line until more safety data is available.

DR. LINDENFELD: I would say the same thing. It should be second-line until we have more data in both the areas we've discussed.

DR. MOYE: Second-line.

DR. MASSIE: Cynthia?

DR. RAEHL: Well, I guess I have a question, what is second-line? Are all calcium blockers second-line compared to diuretics and beta-blockers, JNC V, and those types of things? So, I think it's somewhat of an absurd question.

But having said that, I don't believe it should be second-line. At the same time I would say, as we've already discussed, I think there are a lot of labeling issues regarding contraindications, drugs, other concomitant diseases that need to be addressed. I'm not sure that makes it a second-line therapy in the overall armamentarium.

DR. KONSTAM: Yes, my vote is no. I'm not concerned about the repolarization changes. I don't think it needs to be second line. I'm simply concerned about the LV systolic dysfunction in heart failure.

DR. MASSIE: Very quickly because we've hit the 1:30 threshold. Rob, you voted no on the first vote. What was your reason among the ones that Bob offered?

DR. CALIFF: It's actually a double reason I think. First is I have an underlying concern that there are a lot of people out there with systolic dysfunction that are not known to the practitioner and we've got good epidemiologic evidence I think to back that up. So, I want to know. I think you should know what the risks are when you prescribe a therapy for the patients that you're treating.

And I think the presentation has done a good job of making the case that it's not the quinidine-like effects that are concerning. It's verapamil and diltiazem-like effects. This drug seems to be more like they are.

So, if the MACH 1 results showed a benefit or at least no detrimental effect, then this would be a wonderful first-line treatment. It might even been highly recommended. You're lowering the heart rate, lowering the blood pressure with a great side effect profile.

DR. TEMPLE: No. I understand why it would be good for somebody to have an expanded claim and they understand that too. That's why they're doing the study. But you're now suggesting that they have to require that they pursue that before approval. At least that's what I'm hearing you say.

DR. CALIFF: It would take away the severe restriction which I regard as a fairly nebulous restriction in clinical practice.

DR. GRINES: I have a question. Then, Rob, would you suggest that diltiazem and verapamil be withdrawn from the market then since we don't know really who has LV dysfunction when we initiate therapy in many patients?

DR. CALIFF: Would I advocate that? I'd rather not answer it.

(Laughter.)

DR. MASSIE: I'd like to move on.

JoAnn, why did you vote no?

DR. LINDENFELD: Well, I think for the same reason. I think we just need initial safety data to say that -- we have a lot of other good alternatives for angina and hypertension.

DR. MASSIE: Lem?

DR. MOYE: I just need reassurance that there

may not be some bad sequelae to the findings for repolarization. Clinical trials have shown surprises before, and I just need to know that we don't have a bad surprise waiting for us before we approve the drug.

DR. TEMPLE: But it's the repolarization question.

DR. MOYE: Yes.

DR. KONSTAM: Barry?

DR. MASSIE: I want to move --

DR. KONSTAM: I'm sorry.

DR. MASSIE: You voted yes.

DR. KONSTAM: But I'm sorry. I want to say something.

I just want to say I will not be persuaded by the MACH 1 data that I no longer have to be concerned about patients with LV systolic dysfunction contrary to what Rob said and precisely because I think it's a different background therapy that those patients are on. And I think it's entirely possible, for example, that other calcium channel blockers that have shown neutral to positive effects in the heart failure population have done so because of differences in background therapy as opposed to the fact that it's a different drug. So, I will continue to have the concern about LV systolic dysfunction even if

the MACH 1 data are floridly positive.

DR. MASSIE: Should mibefradil be approved for the treatment of chronic stable angina? And if so, what doses? I guess we really got the doses, but we'll let John vote on this first.

DR. DiMARCO: Yes.

DR. MASSIE: Mike?

DR. WEBER: Yes.

DR. MASSIE: We'll start down there. Marv?

DR. KONSTAM: Yes.

DR. RAEHL: Yes.

DR. MOYE: No.

DR. LINDENFELD: No.

DR. MASSIE: Rob?

DR. CALIFF: No.

DR. GRINES: I'm going to vote yes on this one too. I share some of the same concerns about long-term outcome, but I think that those are things that the FDA perhaps should address prospectively with future applications rather than this particular agent.

DR. MASSIE: So, we've done the doses and we have to do the first and second-line vote again?

DR. LIPICKY: No, I don't think so.

DR. MASSIE: Okay, that's good.

If it is approved, what should the labeling say about mibefradil-associated repolarization changes?

How much detail do you want us to go into?

DR. LIPICKY: I think we know the answer to that. We're okay. Wait a minute. Dr. Temple doesn't think so.

DR. TEMPLE: I wanted to ask a specific question. It obviously has to warn about use in drugs whose metabolism it interferes with. We heard about that.

DR. MASSIE: Could the audience please try to be quiet while we finish our discussion?

DR. TEMPLE: One might also worry about a pharmacodynamic interaction. Was there also a concern about obscuring the ECG? For example, if you used it with quinidine, you might not be able to figure out what the QT actually is. I just wondered whether that was an additional concern or not.

DR. MASSIE: John?

DR. DiMARCO: At the present time, I would recommend that it not be used with drugs that are known to produce changes in the QT associated with morbidity. I just don't think there's any data in this database that relates to that. You'd have to actually look and see what the two did in combination, and there's no information

presented about the combinations.

DR. MASSIE: So, that's virtually any antiarrhythmic would you say?

DR. DiMARCO: Yes, I think virtually any antiarrhythmic. It's going to be a problem, obviously, during treatment of atrial fibrillation, but until the sponsor generates some data with antiarrhythmics, it's going to be difficult.

DR. MASSIE: Any other comments on this one?

DR. LINDENFELD: I still think we ought to give some consideration to the cyclosporin issue. In the renal transplant patients in study 14401 it said, all patients had a two to threefold increase in cyclosporin blood levels. That's a pretty big increase.

DR. MASSIE: So, is the recommendation the labeling point that out?

DR. TEMPLE: We would warn against use with any drug that's metabolized by that system and certainly cyclosporin is one of those.

DR. MASSIE: And I think you've heard some concern which I guess you can take under advisement about LV dysfunction. Is that fair enough?

DR. TEMPLE: We heard that.

DR. MASSIE: Good. We're going to be back here

at 10 after 2:00.

(Whereupon, at 1:34 p.m., the committee was recessed, to reconvene at 2:15 p.m., this same day.)

AFTERNOON SESSION

(2:16 p.m.)

DR. MASSIE: We'll call the meeting to order again and get ready to start. I'm sure that our last remaining committee member or so is going to be in shortly.

The second order of business today is NDA 20-718, Integrilin for the indication of antithrombotic therapy during PTCA. Again, we're going to try to let the sponsor complete their entire presentation before asking questions, and we are going to have to move at a somewhat accelerated pace because we only have a couple of hours for

this whole discussion. So, why don't we get started?

DR. HOMCY: Good afternoon, members of the advisory committee, FDA officials, ladies and gentlemen.

My name is Charles Homcy and I am the Vice President of Research and Development at COR Therapeutics. It's my pleasure on behalf of the company to introduce the agenda on Integrilin today.

Let me start by quickly telling you about COR. COR Therapeutics is a nine-year-old biotechnology company that has focused since its inception on the development of novel therapeutics for acute and severe cardiovascular diseases.

COR's first therapeutic target was the platelet glycoprotein IIb-IIIa receptor. Its goal was to develop an agent which would not only provide incremental antithrombotic protection for patients from the potentially life-threatening complications of coronary angioplasty, but also because of its particular molecular and pharmacologic properties that might achieve this goal without compromising patient safety.

COR searched for an agent that would have three properties. First, since coronary artery disease is a chronic disease and patients frequently require reintervention in months and years of follow-up, COR

focused its efforts on developing a small molecule antagonist which would, by its very nature, not pose an immunogenic potential and thereby allow readministration to proceed safely.

COR wanted this molecule to have two other properties as well: a short plasma half-life and rapidly reversible receptor binding kinetics allowing platelet blockade to be rapidly turned on, but also rapidly reversed if bleeding became a problem.

As you are aware, COR is seeking approval for Integrilin as an adjunct to PTCA for the prevention of acute ischemic cardiac complications related to abrupt closure of the treated coronary vessel. Specifically these complications can include the irreversible ones such as death in myocardial infarction, as well as the need for urgent intervention.

In preparing to come to this advisory committee, we have been well aware of the issues related to our demonstrating substantial proof of efficacy based on the results of the IMPACT II trial. I am referring to the fact that although one of the two drug treatment arms in this single pivotal trial met the protocol-specified level for a significant reduction in the primary efficacy endpoint, this effect was not as robust as predicted.

Specifically, the IMPACT II trial was sized to detect with 80 percent power a 33 percent reduction in ischemic events at 30 days versus placebo, while in actuality the observed drug effect was closer to 20 percent.

With these issues in mind, our seeking approval for Integrilin is based on a body of data which demonstrates that the drug clearly works. By this, I mean that it incrementally adds antithrombotic protection for patients during a coronary angioplasty over that which is possible with standard heparin and aspirin and, secondly, that this pharmacologic effect translates into a clear clinical benefit for patients.

In your evaluation of efficacy, we realize that these are the two key points that must be convincingly supported by the data: first, that the drug works and, more importantly, that patients benefit. You will see data today that demonstrates that the thrombotic complications of angioplasty, specifically death, MI, and the need for urgent intervention, were immediately and robustly decreased in both Integrilin-treated cohorts, and when one looks thereafter, this benefit persisted.

Just as importantly, this clinical benefit was achieved without incurring a safety penalty. COR's goal in introducing this new therapy was not only to show that it

could add antithrombotic protection for platelets by way of IIb-IIIa blockade, but also that this could be done safely by identifying that portion of the dose-response curve which had the best opportunity to be both effective and safe.

It is Friday afternoon, and I realize that ours is the fourth application to have been reviewed by you in the past two days. In this spirit, we would like to keep our presentation short and we will and therefore have geared our agenda to get at the issues.

Before the efficacy data are presented, it will be valuable for you to hear from Dr. David Phillips, a scientist at COR who first cloned and characterized the IIb-IIIa receptor. He will review the rationale as to why the blocking of this molecule on the platelet surface offers the best opportunity for abrogating platelet-mediated thrombosis. He will briefly tell you about the development of Integrilin and focus on the pharmacologic features that were engineered into this molecule during its development. Understanding the properties that were sought has implications for the efficacy and safety data that was achieved with this molecule.

Dr. Michael Kitt, the Vice President of Clinical Research at COR Therapeutics, will present the

efficacy data and his will constitute the bulk of COR's presentation today.

Dr. Kerry Lee of Duke University, the biostatistician for the IMPACT II trial, is available for questions that might arise from Dr. Kitt's presentation.

Dr. Todd Lorenz of the Clinical Research Group at COR will then briefly summarize the safety data.

I will conclude with a summary of all the data supporting the positive benefit-to-risk profile of Integrilin.

In light of the questions that have been posed to the committee by the FDA, among other participants that are here with the COR group -- and these are listed in your briefing book -- is Dr. Robert Harrington, a cardiologist at Duke University, who was an investigator in the IMPACT II trial and is a principal investigator of PURSUIT, our own stable angina trial. He is available in particular to address the issue of the relevance of the PURSUIT trial to your present deliberations.

I'll ask David Phillips to come up to the podium now.

DR. PHILLIPS: Good afternoon.

During this preclinical presentation, I'd like to first talk about IIb-IIIa and discuss its role in

thrombosis and hemostasis mediated by platelet aggregation and why IIb-IIIa is an attractive drug discovery target; next, the discovery and properties of Integrilin and why Integrilin is of value for the treatment of acute coronary syndromes; and finally, the preclinical pharmacology of Integrilin, which has established its antithrombotic activity and the pharmacodynamic correlates which were used for dose selection for the IMPACT II trial.

We're all aware that vascular injury induces platelet aggregation and subsequent thrombus formation. Endothelial cells normally provide the protective barrier that prevents this from occurring. When these are removed by procedures such as angioplasty, adhesive proteins are exposed that cause platelet adhesion and subsequent aggregation. Occasionally this can become occlusive when stabilized by thrombin.

A point I'd like us to focus on is that a thrombus is essentially composed of the same components as is the hemostatic plug, and in developing an antithrombotic strategy, it's important to inhibit aggregation with a minimal effect on hemostasis.

Platelet aggregation is mediated by the IIb-IIIa complex which exists on the surface of unstimulated discoid platelets. When platelets are activated by agents

such as collagen, ADP or thrombin, platelets become activated, as does the receptor function for IIb-IIIa. Aggregation is mediated by fibrinogen and to some extent von Willebrand's factor, and it is this bifunctional activity of adhesive proteins that allows this to occur.

Our objective is to identify an inhibitor of IIb-IIIa, and it's important to remember that this will inhibit aggregation irrespective of the agonists that activate platelets and therefore block the final common pathway leading to platelet aggregation.

COR used a novel drug discovery strategy in order to identify Integrilin. Several years ago, it was identified that snake venoms contain disintegrins which are IIb-IIIa antagonists and therefore block platelet aggregation. These are nonspecific agents and react with other integrins, for example, alpha-v beta-3, and alpha-5 beta-1.

In order to identify a specific inhibitor, COR screened some 60 snake venoms and found one, the southeastern pygmy rattlesnake, which had a protein we termed Barbourin which was a specific IIb-IIIa inhibitor. From the structural information that was provided by analysis of this, Integrilin was synthesized, which retained the integrin specificity of IIb-IIIa.

IIb-IIIa blocks platelet aggregation in a reversible manner, and this is illustrated on this slide. Here baboons are infused with an increasing dose of Integrilin, and we see the dose-dependent inhibition of platelet aggregation.

To demonstrate this reversible nature of Integrilin, baboons were infused with this dose of Integrilin at a constant infusion rate, and we can see a rapid inhibition of platelet aggregation, and of interest, when the infusion of Integrilin is discontinued, we see a rapid restoration of platelet function.

This restoration of platelet function is important as it allows for restoration of normal platelet function if bleeding, for example, would occur in an individual receiving Integrilin or if a secondary procedure would have to be performed.

In evaluating the antithrombotic activity of Integrilin, we realized that none of the animal models that we examined would directly mimic the antithrombotic activity of Integrilin, the antithrombotic activity that's created following an angioplasty procedure. Therefore, we used a variety of different animal models, and these are all illustrated here. It's in the dog, in the baboon, and indeed we found that Integrilin would inhibit thrombosis in

all of these.

We focused on three, however, which proved to be of value in arriving at the dose of Integrilin that would inhibit thrombosis with a minimal effect on bleeding, and I will summarize some of those data to illustrate that point here.

These are the three models that are listed here at the top. All of these models are resistant to heparin. The anodal current model and the A-V shunt model in baboons in addition are resistant to aspirin.

It was observed that infusion of Integrilin to achieve 75 to 95 percent inhibition of platelet aggregation would cause a potent inhibition of platelet aggregation. This was achieved with only a modest effect on the bleeding time in these animals. These data suggested, therefore, that infusions of Integrilin can be achieved that would be antithrombotic, but would only have then a modest effect on the bleeding time in these animals.

I think it's instructive at this point to summarize these pharmacodynamic parameters on the doses that were used in the IMPACT II trial. These are illustrated here. These are data from the IMPACT high/low study which was a dose-ranging study in angioplasty patients. The two doses used in the IMPACT II trial are

illustrated at the bottom.

First, it was observed that the bolus infusion achieved approximately a 95 percent inhibition of aggregation and this high level of inhibition of aggregation maintained a blockade of platelet function during the critical stages following angioplasty where most thrombotic events occurred.

At the termination of infusion, the two doses achieved an 80 to 65 percent inhibition of aggregation with considerable overlap. Based on our preclinical study, it was anticipated that these doses would be antithrombotic.

Analysis of the simplate bleeding time in these individuals showed that these doses of Integrilin approximately doubled the bleeding time expected to be well within the safe range. It's of interest that following termination of an infusion, normal bleeding time would be obtained again within approximately 1 hour, again demonstrating the reversible nature of Integrilin.

So, in summary, I've discussed that IIb-IIIa mediates thrombosis and hemostasis and is involved in the final common pathway of platelet aggregation.

Integrilin was discovered as a high affinity IIb-IIIa inhibitor, which is integrin-specific.

Preclinical pharmacology has established that

Integrilin has a titratable antithrombotic activity in multiple models and that Integrilin is antithrombotic but with a minimal effect on the bleeding.

Thank you. I'd like now to turn the podium over to Dr. Michael Kitt who will review the efficacy data on the IMPACT II trial.

DR. KITT: Good afternoon.

I'm here today to present an overview of the clinical development program of Integrilin in the treatment of patients undergoing coronary angioplasty for the prevention of acute ischemic events. The efficacy presentation will cover the clinical rationale for the development of Integrilin in this indication, the design of the IMPACT II study, and finally the data demonstrating the efficacy of treatment with Integrilin.

As you're aware, the results of the primary endpoint, as mentioned by Dr. Homcy, are less than predictive for the recommended Integrilin dosing regimen. Therefore, the data presented will not only address the primary endpoint, but will also demonstrate key corroborating evidence for efficacy. In particular, the demonstration of the antithrombotic effects in preventing abrupt closure and acute ischemic events at 24 and 48 hours.

After my presentation, Dr. Lorenz will review the drug safety profile which has been consistently excellent throughout the clinical development program.

Coronary angioplasty is a common procedure with over 500,000 interventions performed in the U.S. annually. Its success is primarily related to the relative ease in which the procedure can be performed and the marked relief in symptoms that angioplasty provides.

There are two serious complications of coronary angioplasty. Thrombotically mediated abrupt closure is a devastating and life-threatening event that can occur rapidly after the intervention. It is this complication that is the focus of the development program of Integrilin.

Restenosis, on the other hand, is a costly complication of coronary angioplasty. It affects patient quality of life and frequently requires rehospitalization for repeat intervention. The data will show that Integrilin is not recommended for the prevention of restenosis.

The rationale for the clinical development of Integrilin was based on literature reports that thrombotically mediated abrupt closure was the major cause of acute ischemic events in patients undergoing coronary angioplasty.

The preclinical models that Dr. Phillips has just presented have established that Integrilin's effect is titratable to the antithrombotic activity and the effect is rapidly reversible.

It was proposed, therefore, that Integrilin could prevent abrupt closure and thereby reduce the incidence of acute ischemic events in patients undergoing the procedure.

Furthermore, the clinical development of Integrilin was focused on achieving incremental antithrombotic protection over standard therapy with aspirin and heparin without increasing the risk of bleeding.

The phase III study entitled Integrilin to Minimize Platelet Aggregation in Coronary Thrombosis, or the IMPACT II study, was a multi-center, double-blind, randomized, placebo-controlled trial. The study was conducted across 82 investigational sites in the U.S. covering a broad range of institutions from primary care to tertiary hospitals. It therefore represents the spectrum of the practice of interventional cardiology.

IMPACT II was the single largest study of coronary angioplasty ever conducted in patients of all risk strata. The study was designed to enroll a broad patient

population representing real clinical practice and contained few exclusion criteria for enrollment into the study.

The IMPACT II coordinating center was responsible for generating the randomization code, drug allocation, and conduct of the interim analyses and study monitoring. The Data and Safety Monitoring Committee was responsible for performing ongoing safety reviews and for the interim analyses of efficacy. The Clinical Events Committee provided blinded, independent review and confirmation of the efficacy and important safety results.

The dose selection in the IMPACT II study was based on the results derived from the described preclinical models of thrombosis, as well as two phase II studies in coronary angioplasty.

One of these studies, the first IMPACT study, was conducted in 150 patients undergoing coronary angioplasty. The efficacy results of this study showed a positive trend and led to the high/low study which resulted in the identification of the doses for the IMPACT II trial.

Most events were predicted to occur shortly after deployment of the interventional device. Therefore, we searched to find a common bolus dose that would provide substantial inhibition of platelet function during this

critical period. In this study, we chose a common bolus dose for both Integrilin regimens of 135 micrograms per kilo.

It was also known from previous studies that prolonged administration of drug was necessary. However, a primary focus of this development program was also to achieve an antithrombotic effect without compromising patient safety, in other words, exploring the safest effective dose. Therefore, a continuous infusion of 20 to 24 hours of two different doses of Integrilin, namely .5 microgram per kilo per minute and .75 microgram per minute were chosen for the IMPACT II study.

The primary endpoint in this study was chosen to capture the clinically relevant complications of coronary angioplasty. It was composed of any of the following occurring within 30 days of enrollment: death from any cause, myocardial infarction defined as new Q-waves on the ECG or a prespecified elevation of cardiac enzymes, or severe symptomatic myocardial ischemia necessitating urgent coronary artery bypass surgery, repeat coronary angioplasty, or stent placement for abrupt closure.

Although the principal antithrombotic activity of Integrilin was expected to occur during drug

administration, the primary endpoint was measured at 30 days to assure that there was no reversal of this beneficial effect over time.

The incidence of other clinically relevant endpoints was also captured. These include angiographically observed incidents of abrupt closure, the efficacy endpoints of death, myocardial infarction, or repeat urgent intervention at 24 and 48 hours, as well as an analysis of the long-term benefit achieved at 6 months.

In addition, the principal investigators in the study were asked to assess the efficacy endpoint at 30 days.

The study was designed to provide an 80 percent power to detect a 33 percent reduction in the primary endpoint from placebo.

The expected placebo event rate at 30 days was 11 percent. This led to the choice of a sample size of 3,500 patients. This was increased by the Data and Safety Monitoring Committee to 4,000 patients based on an interim efficacy analysis which allowed an adjustment to the sample size if the event rate in the placebo group was less than expected.

Pairwise comparisons of each Integrilin dosing regimen to placebo were specified in the protocol, and

although there may be other opinions as to the magnitude of the alpha adjustment, we chose an alpha of .035 to account for the two comparisons.

As noted in the briefing document, the recommended dosing regimen of Integrilin is a bolus of 135 micrograms per kilo at a continuous infusion of .5 micrograms per kilo per minute.

In addition, the results of the randomized and treated patient analysis were described. The results of the randomized patient analysis were similar to the results of the treated patient analysis. By design the randomization assignment was performed before the patient was brought to the cath lab. This was done to minimize disruption in the routine processes of care. However, this resulted in 139 patients being randomized but not treated.

Since these patients could be eliminated without the introduction of bias, a treated patient analysis, which was specified prior to unblinding, was selected as a more sensitive way of looking at treatment effect. Therefore, I will focus my comments on the treated patient analysis.

These are the key points I will make for the evaluation of efficacy. The primary endpoint was chosen to demonstrate whether the antithrombotic activity that was

expected early after the intervention resulted in a durable benefit to patients.

The demonstration of the antithrombotic effect can be evaluated by the incidence of abrupt vessel closure, as well as by the clinical sequelae of this process measured in the first few days following the intervention.

Clinical benefit was measured by the sustained reduction in the serious complications of coronary angioplasty over time. This will be demonstrated by the treatment effect in decreasing death or myocardial infarction over the entire study period.

Finally, I will also present data demonstrating replication of results within this large study, as well as the consistency of the results across treatment groups.

These are the results of the IMPACT II study. First, the results of the analysis of the primary endpoint at 30 days.

There was an 11.6 percent incidence of the primary endpoint in the placebo group. This confirms that even in the study that included both elective and high risk patients, the incidence of acute ischemic events continues to be high.

There was a 14 to 22 percent relative reduction in the primary endpoint in patients treated with Integrilin

compared to placebo. The benefit from treatment with Integrilin in the 135/.5 group met the protocol-defined level of significance.

Although these results are less than expected, they still fell within the range of positive outcomes. Therefore, the primary endpoint does provide evidence of efficacy as it was chosen to confirm that the antithrombotic effect was sustained.

Let's turn to the demonstration of the drug's antithrombotic effect.

Early time points demonstrate the clear antithrombotic activity of Integrilin. Abrupt closure, the result of endothelial disruption by the interventional device, is responsible for many of the acute ischemic events seen after coronary angioplasty. Integrilin reduced the incidence of abrupt closure.

In this study, 5.1 percent of patients in the placebo group sustained an angiographically observed abrupt closure. Treatment with both doses of Integrilin significantly reduced the incidence of abrupt closure by 35 to 45 percent. This important effect on the prevention of abrupt closure is consistent with the proposed mechanism of action of Integrilin and demonstrates Integrilin's clear antithrombotic effect.

In this study, abrupt closure was strongly associated with ischemic complications with a greater than 45 percent incidence of the primary endpoint in patients who had abrupt closure. Preventing abrupt closure, therefore, translates directly to patient benefit in a reduction in ischemic events.

As previously noted, Integrilin decreased the incidence of ischemic events early on. This is a Kaplan-Meier curve which shows the frequency of the efficacy endpoint over 48 hours. The yellow line describes the placebo group; the blue and green line, the two Integrilin treatment arms. Three key points can be derived from this slide.

First, as predicted, most of the events occurred early. In the placebo group, about 70 percent of the events had already occurred by 6 hours. Specifically, 84 percent of all events that were to occur at 30 days had already occurred at the end of 48 hours.

Second, the benefit of treatment with Integrilin was robust. This was a marked separation between the placebo-treated patients and the Integrilin-treated patients at these early time points. At 24 hours, there was a significant decrease of 28 to 31 percent in the efficacy endpoint in patients treated with Integrilin

compared to placebo.

And third, the effect was replicated between the two Integrilin dosing groups, again in almost 2,600 patients, during the first 48 hours.

These results confirm that platelet mediated thrombosis plays a significant role in the occurrence of acute ischemic events in patients undergoing coronary angioplasty and that these events can be prevented by inhibition of platelet function with Integrilin.

The 30-day endpoint was chosen to examine if the clinical benefit of treatment that occurred early after device deployment was not reversed over time. This Kaplan-Meier plot shows the frequency of the primary endpoint over 30 days. These data demonstrate the following.

First, as described the vast majority of events occurred early on.

Second, there continues to be a clear separation between the two Integrilin groups and the placebo group. This treatment benefit which was seen early is maintained to 30 days.

Third, as mentioned, 84 percent, or 332 of the total 395 events that were measured at 30 days, had already occurred at 48 hours. Therefore, the magnitude of the relative reduction was diluted by events that occurred well

after treatment was discontinued.

These results of the primary endpoint confirm that the clinical benefit of treatment with Integrilin was sustained.

Long-term outcomes were measured in this study over 6 months. The endpoint was slightly different from the 30-day endpoint in that any revascularization is included rather than only urgent interventions. This is important to note because restenosis was expected to be the most frequently occurring event following coronary intervention.

As you can see, Integrilin had no effect on restenosis in this study. There was more than a doubling of events from the end of the first month to the end of the sixth month with roughly similar increases in all three treatment groups. The vast majority of these events in all groups was repeat revascularization procedures. It is important to note that even 6 months after treatment with Integrilin, there is no reversal of the acute benefit in that the event lines do not cross.

The major benefit, therefore, was the reduction in the irreversible complications of coronary angioplasty, death or myocardial infarction. I will be presenting three Kaplan-Meier plots demonstrating this benefit over time by

treatment with Integrilin.

This plot of the frequency of death or myocardial infarction over 48 hours demonstrates a key result of this study. There was a reduction from 7 percent in the placebo group to 5.5 percent with treatment with Integrilin, an absolute reduction of 1.5 percent in the incidence of death or myocardial infarction after 24 hours. This benefit on the irreversible complications of coronary angioplasty was replicated in both Integrilin treatment groups. Thus, antithrombotic therapy with Integrilin resulted in a real clinical benefit over standard antithrombotic therapy.

The incidence of death or myocardial infarction was also reduced by the same magnitude at the primary endpoint at 30 days with treatment with Integrilin.

Finally, at 6 months, a point distant from treatment, the data demonstrate that this important clinical benefit to patients, patients treated with Integrilin maintained this benefit continuing to show the same absolute reduction of death or myocardial infarction compared to patients only treated with aspirin or heparin. Thus, the clinical benefit achieved with Integrilin therapy was not lost over time.

These data demonstrate replication within the

study as both Integrilin treatment regimens demonstrated a similar reduction at all time points.

To explore the consistency and replicability of treatment with Integrilin, additional analyses were performed. These included the assessment made by the investigator of treatment benefit, combining the two treatment groups, and examining the consistency of effect in the components of the primary endpoint and across prespecified subgroups.

The principal investigators were asked to determine in a blinded manner if a patient met any of the components of the primary endpoint over the 30-day period. The investigators' assessment is likely to represent events that were clinically apparent. In other words, if the event was important enough for the investigator to see, then the event was called.

The results of the investigators' assessment of the benefit of treatment with Integrilin was consistent with the primary endpoint as determined by the Clinical Events Committee. In fact, the investigators' assessment showed a slightly greater treatment effect.

There was a significant decrease in the incidence of death, myocardial infarction, and urgent intervention at 30 days, as assessed by the investigators,

with Integrilin therapy at the recommended dosage. Even with the difference in the incidence of myocardial infarction in the investigators' assessment, the benefit of treatment was seen. This similar benefit of treatment with Integrilin by this assessment adds to the consistency within this data set.

Consistency of benefit can also be observed by examining the treatment effect of Integrilin in predefined demographic subgroups. Odds ratios are shown to compare treatment effects across subgroups. These odds ratios express the estimated risk of having an event with Integrilin therapy relative to the risk of having an event with placebo treatment. The estimated odds ratio for each group is shown as a point, and the 95 percent confidence intervals are shown by the horizontal lines extending from the point. An odds ratio of less than 1 corresponds to an observed treatment benefit with Integrilin. The odds ratio for the primary endpoint in prespecified subgroups were close to the odds ratio for the entire group of patients treated with the recommended dosing regimen of Integrilin.

The principal point of this slide is that although these subgroup analyses are not powered to demonstrate individual treatment differences, the consistency of the odds ratio estimates adds to the body of

evidence for the overall efficacy of Integrilin.

To further explore the treatment effect, both Integrilin dosing regimens were combined and compared to placebo. Shown here are the results of this analysis.

There was an 18 percent reduction with Integrilin treatment at the primary endpoint compared to placebo, with a p value of 0.046. The odds ratio estimates for the two Integrilin treatment groups are similar and the confidence intervals overlapping, thus demonstrating the consistency between the two dosing groups in the combined analysis.

Consistency of treatment effect can be examined using the components of the primary endpoint. Both Integrilin groups decreased the incidence of all components of the primary endpoint compared to placebo. Specifically, there is a consistent decrease in all components in the primary endpoint in both Integrilin groups.

Death was unusual in this study. The most common event was myocardial necrosis. As already noted, there was a treatment benefit in this component at all time points. The demonstration that there are no differential treatment effects in the components of the primary endpoint is consistent with Integrilin's primary effect.

Let me summarize the evidence for efficacy.

Treatment with Integrilin did what was predicted and this resulted in a tangible clinical benefit. The efficacy analyses of the IMPACT II study demonstrate four key points.

First, although the results of the primary endpoint were less than expected, they did meet the protocol-defined level of significance. In addition, there was ample evidence that this result was not by chance. Almost every analysis at every time point points to a benefit for treatment with Integrilin.

Second, Integrilin demonstrated potent antithrombotic activity in man. There was a 45 percent reduction in abrupt closure in patients treated with the recommended dosage of Integrilin. This is consistent with the main biological premise for drug development.

Third, the clinical manifestation of the antithrombotic effect of treatment was seen in the rapid and robust reduction in death, myocardial infarction, and urgent intervention in the first 24 to 48 hours after the coronary intervention.

And fourth, the irreversible complications of death and myocardial necrosis were prevented in patients treated with Integrilin. There was an absolute reduction of 1.5 percent in death or MI that occurred after 24 hours.

This result was not lost over time.

Finally, this large, multi-center single study was designed to provide internal replication of results. The two Integrilin treatment regimens had the same bolus dose and a similar infusion. Therefore, both were expected to have similar efficacy results. This can be seen in the efficacy results with the benefit of both Integrilin dosing regimens similar in reducing the incidence of abrupt closure, decreasing the incidence of ischemic events at 24 and 48 hours.

The results of the primary endpoint are also consistent with the similarity of benefit. The more striking similarity in the results of the two dosing groups comes in the reduction of death or myocardial necrosis at all time points.

This, combined with Integrilin's excellent safety profile, resulted in improved overall positive outcomes in patients treated with Integrilin who underwent coronary angioplasty and points to an excellent benefit-to-risk assessment.

Thus, Integrilin is effective as an adjunct in patients undergoing coronary angioplasty in reducing acute ischemic events.

I'd like to now invite Dr. Todd Lorenz who will

describe the safety results of the IMPACT II study.

DR. LORENZ: Good afternoon. It's my pleasure to present the safety results from the IMPACT II study to the members of the Cardio-Renal Advisory Panel.

At the beginning of the clinical program, the concept of GP IIb-IIIa blockade as a therapeutic target in patients undergoing coronary angioplasty was new. There was great concern regarding the clinical implications of adding a potent platelet blockade to patients who are already receiving heparin and aspirin. Therefore, the IMPACT II study was designed to yield efficacy without compromising safety.

Integrilin is a potent, platelet-directed antithrombotic agent. Therefore, special attention was given to several theoretical safety concerns in the study design.

In particular, the exacerbation of bleeding complications was of concern because of the pharmacologic action of the drug.

Secondly, since Integrilin binds to platelets, the possibility existed of either enhanced clearance or marginalization of the platelets resulting in thrombocytopenia. For that reason, platelet counts were obtained every 6 hours while patients were on study drug.

Finally, as a small molecule incorporating only seven amino acids, Integrilin was designed to pose a minimal risk of immunogenicity. However, the possibility of an unexpected immune response was investigated by a substudy within IMPACT II that collected samples for analysis of anti-Integrilin antibodies on the first 10 patients enrolled at each site.

In considering the effect of Integrilin on safety, it's important to recall that Integrilin was added to standard antithrombotic medications. In the IMPACT II study, this included a bolus of weight-adjusted heparin of 100 units per kilogram, and patients were kept at a target activated clotting time of between 300 and 350 seconds. Patients also received aspirin.

Bleeding complications in the IMPACT II study were primarily scored using the TIMI Bleeding Scale. That's an objective measure of blood loss that is determined primarily by changes in hemoglobin concentration and designates bleeding as either being major or minor.

Major bleeding represents a significant morbidity to the patient. It preserves a potentially life-threatening situation and often is associated with a need for blood transfusion.

In the IMPACT II study, the incidence of major

bleeding was similar in the placebo group and both Integrilin-treated regimens. Therefore, the addition of potent GP IIb-IIIa blockade to standard antithrombotic therapy did not increase the incidence of major bleeding in patients undergoing angioplasty.

The most serious bleeding complication of antithrombotic therapy is, of course, intracranial hemorrhage. This complication was actually quite rare in the IMPACT II study, with an overall incidence of 0.1 percent. Specifically, that included 1 patient in the placebo group, 1 patient in the .5 infusion group, and 2 patients in the .75 infusion group.

The need for transfusion is also an indicator of the severity of bleeding. Transfusion represents a morbidity in itself in fact in that it confers a finite although limited risk of acquiring a transmissible virus.

In the IMPACT II study, Integrilin was not seen to increase the need for red blood cell transfusion in the overall study compared to patients receiving placebo. Similarly, the incidence of platelet transfusions was very low among all three treatment groups.

The pharmacologic effect of Integrilin on bleeding was limited to an increased incidence of minor bleeding events which occurred in 9.3 percent of patients

in the placebo group compared to 11.7 and 14.2 percent of patients in the Integrilin-treated groups. Compared to major bleeding events, minor bleeding events are generally considered reversible, are of short duration, and do not result in important clinical sequelae.

Discontinuation of study drug due to bleeding was also more common among patients receiving Integrilin. Specifically, 1.9 percent of patients in the placebo group discontinued due to bleeding compared to 3.5 and 4.3 percent of patients in the Integrilin-treated groups.

Please note, however, that this difference is not due to patients experiencing major bleeding events, but rather milder forms of bleeding. This observation is entirely consistent with the pharmacology of Integrilin in that the rapid receptor off-rate and short half-life of the drug allowed physicians who noted unusual bleeding in patients to discontinue study drug and prevent an event in progress from becoming major.

There were no laboratory abnormalities associated with Integrilin therapy, including electrolytes, hepatic transaminases, indices of renal function or leukocytes. In particular, Integrilin was not associated with thrombocytopenia. There was no difference either in significant decreases from baseline or when one examines

progressively severe nadir counts of platelets across treatment groups. Therefore, although Integrilin is a platelet-directed agent, it was not associated with an increased risk of thrombocytopenia.

Finally, we employed a standard, indirect ELISA that was sensitive to all isotypes of human immunoglobulins to detect an anti-Integrilin immune response. Serum that was collected at baseline and 30 days in 390 patients enrolled in the study were analyzed for evidence of an immune response and none was found.

To expand on these findings, a small clinical pharmacology study of repeat dosing, separated by a 28-day period, was conducted in 21 normal volunteers. In that study there was no evidence of either a primary or an anamnestic antibody response.

In summary, the IMPACT II study, which comprises almost 90 percent of the 3,671-patient Integrilin safety database, establishes the safety of Integrilin with respect to major bleeding, transfusion requirements, thrombocytopenia, and immunogenicity.

I'd like to turn the podium back over to Dr. Charles Homcy who will provide our concluding remarks.

DR. HOMCY: In summarizing what you have heard today, I will focus on certain key issues.

First, does the available data on Integrilin clearly support the conclusion that the drug exerts a prominent antithrombotic activity in man? Does the drug work?

We have presented strong data in support of this point. Abrupt closure as a hallmark of angioplasty induced thrombosis was significantly reduced overall by 40 percent, and this effect was replicated in both dosing arms.

However, a second and clearly the most important question is how this translates into a clinical benefit for patients. The goal of the IMPACT II study was to demonstrate that Integrilin treatment could prevent the serious clinical sequelae that result from the thrombotic complications of coronary angioplasty. As you have heard today, a significant 30 percent reduction in death, MI, and the need for urgent intervention was realized in the first 24 to 48 hours after the angioplasty procedure in patients treated with Integrilin. Again, this effect was replicated in both Integrilin arms representing over 2,600 Integrilin-treated patients.

The effect of the drug was clear cut and was most prominently seen in the immediate hours during and after the angioplasty when the vast majority of

thrombotically mediated events occurred. The drug worked when it was supposed to work.

The worst of these ischemic complications, of course, are the irreversible ones: obviously, death but also importantly myocardial necrosis. Drug treatment reduced these types of complications by 22 percent at 24 hours, from 7 percent in the placebo group to 5.5 percent in the Integrilin-treated cohort. This absolute reduction of 1.5 percent in death or MI was maintained at a nearly identical level at 30 days and 6 months, an effect again replicated in both arms of the study. Simply put, the initial reduction in the irreversible complications of angioplasty seen in both Integrilin-treated cohorts was not lost.

It is important to note that even in elective patients, the incidence of death or MI was nearly 9 percent, more in the MI of course. As a cardiologist, this was a surprising result to me, and I believe a very important result. The data clearly tells us that elective patients in fact are not low risk patients. Myocardial infarction occurs at a rate of almost 8 percent in this group we call elective. An effective therapy that physicians are confident about using because it is safe, because it provides them with a high level of control -- in

this case, I'm specifically referring to the reversibility of this drug -- would likely be used in routine clinical practice and therefore would benefit this large number of patients we call elective. Integrilin has this profile.

As we have indicated earlier, the magnitude of the relative reduction in the primary efficacy endpoint of this study was less than predicted, indicating that the early more robust effect in the efficacy endpoint was diluted by additional endpoints that continue to occur in all cohorts quite distant from the period of drug infusion.

Nonetheless, a parsimonious analysis of all the data in the IMPACT II trial argues that the Integrilin-treated patients clearly benefitted and their outcome was improved as compared to patients treated with the standard regimen of aspirin and heparin.

These were hard endpoints, and in the case of MI, a permanent complication that cannot be reversed, the drug achieved these effects without doing harm to patients.

Again, it is important to emphasize that its safety profile was excellent in the setting of routine clinical practice in combination with standard heparin and aspirin therapy. The IMPACT II trial was a very large trial carried out in 82 centers and it was a stringent test of Integrilin, both its efficacy and safety, because it

tested this drug in routine clinical practice across a spectrum of clinical settings using routine heparin and aspirin regimens and using a multitude of different interventional devices. The effects we have seen in IMPACT II, both safety and efficacy, can therefore be expected to translate into the real-life situation.

Integrilin is the first small-molecule IIb-IIIa receptor antagonist to be thoroughly investigated in the clinical setting of coronary angioplasty, and as such it provides certain valuable features. Clearly it is rapidly acting, but its effects are also rapidly reversible, and as a result of its small molecular weight, it has shown no immunogenic potential.

Integrilin thus provides a pharmacologic and pharmacokinetic profile not presently available to the cardiologist. These are a set of features which afford clinicians a new level of control. This is why COR designed the small-molecule antagonist.

In concluding, my main points have been this small-molecule IIb-IIIa antagonist is a therapeutic advance because it brings useful and predictable pharmacologic features to clinical practice which help to ensure patient safety. Most importantly, however, the drug reduces the clinical sequelae of the thrombotic complications of

angioplasty, in particular death and MI. The data presented today should also provide confidence to physicians and patients alike that this benefit can be obtained at a minimal to no safety cost.

I would like to end by thanking the advisory panel members and the FDA officials for all of their time and effort in reviewing our application. I and the rest of the COR team are available to answer questions at this point. Thank you.

DR. MASSIE: Thank you very much.

Marv, do you want to start off the questioning?

DR. KONSTAM: Sure. I have a few questions.

First of all, by way of clarification, maybe you said it, but the 6-month follow-up data was a different endpoint, was it not?

DR. KITT: Yes. The 6-month endpoint was the incidence of death, myocardial infarction, and any intervention.

DR. KONSTAM: Right, okay. Can you just comment about what implication that might have?

DR. KITT: It's felt that the primary endpoint, which was only capturing the death, MI, and urgent intervention, was capturing events that are relevant to the actual procedure itself. Looking at any intervention, at

the time that we designed this study, we were looking at effect on restenosis and therefore were looking at all interventions. But as you saw from the data, that was not true.

DR. KONSTAM: Again, maybe you said it, but out of curiosity, if you take that not-prespecified endpoint and look back at it at 30 days, is it statistically significant between the groups?

DR. KITT: No, it's not.

DR. KONSTAM: The next question I have is, could you just comment on why did you choose the .035 p value to prespecify?

DR. KITT: Sure. We have Dr. Kerry Lee from Duke University who's prepared to answer that.

DR. LEE: I'm Kerry Lee.

The .035 was chosen as an intermediate position actually between the conservative Bonferroni adjustment and its inherently increased sample size requirements versus the alternative and equally valid point of view that in studies like IMPACT II which are efficiently designed to obtain information about multiple doses, statistical methods can be used to preserve a two-sided type 1 error rate of 5 percent for each comparison.

This has been persuasively argued actually in

the literature by well-known clinical trial statisticians such as David Byar and Steve Piantadosi who contend that one should not necessarily be penalized in a study where efficacy information is obtained about two doses because if those two individual doses had been studied in two separate trials, adjustment to preserve the overall type 1 error rate across those two trials would not be required.

Other statisticians actually have contended that statistical methods to preserve a study-wide type 1 error rate ought to be replaced by adjustments through informal or formal overviews of all of the available safety and efficacy information at the time of an NDA review. This type of an approach actually recognizes that evidence of a treatment benefit in one arm is strengthened, rather than weakened, by corroborative evidence of an effect in another arm.

So, if you ask the question, does the .035 limit the study-wide type 1 error rate for these two comparisons to .05, the answer is no, it does not. In fact, as outlined in the document prepared by the statistical reviewer, it's on the order of .064.

But what you as a committee obviously have to consider in evaluating this information is whether these results represent a type 1 error or whether the differences

observed in this trial are actually real. There are two or three points I would encourage you to consider in that deliberation.

One, as Dr. Kitt has pointed out, the comparison of low-dose Integrilin versus placebo did indeed reach the prespecified significance level of .035.

Second, if you combined the Integrilin doses into a pooled treatment arm, compared that with placebo in a single comparison, that also achieves statistical significance.

Third, if one examines the data, the MI data, as measured and reported by the clinical investigators, the comparison of the combined endpoint of the low-dose arm versus placebo in both the all-treated patients and the all-randomized patients, it's statistically significant at the more conservative Bonferroni level of adjustment.

DR. KONSTAM: Yes, I'd like Lem to comment.

DR. MOYE: I can't take issue with the decision of .035 because clearly the choice of the level of alpha, when you are facing prospectively a multiple comparison issue, is disputatious. It's hard to find all statisticians to agree on anything and they certainly won't agree on this.

(Laughter.)

DR. MOYE: However, you did make the decision. I understand the reasoning and it was made prospectively. So, I think that that is the substantial weight of the argument here. So, I actually have no issue with the choice of .035.

DR. KONSTAM: Thanks.

I have a number of questions, a couple of questions, about the bleeding complications.

The first is -- and maybe I'm just confused or missing something -- there's a separate analysis about adverse events, and there's something called serious adverse bleeding events that appears to be more common in the Integrilin-treated groups than in placebo. Why am I confused about this?

DR. KITT: Adverse events are defined in multiple ways typically in clinical trials. I'm not certain of the specific table you're looking at. Actually, if you could tell us exactly which one it is.

DR. KONSTAM: Well, what I'm looking at is the medical review, page 79, which is titled Serious Adverse Events, and it's an analysis of that. That's what I'm referring to.

DR. KITT: Right. We defined adverse events, obviously, in a whole host of ways. When the investigator

reported an adverse event, there was a definition, and the serious definition is the FDA definition of an adverse event. We used an algorithm to come up with that definition.

I'm not sure exactly of the question, though. You're saying there's a difference between --

DR. KONSTAM: Well, I just wondered if you could comment on it. I guess it's a separate analysis. I understand it's reported adverse events and I assume that it required some different form of judgment on the part of the investigator than was done based on the prespecified analysis. And it comes out a little different. I don't know whether it's statistically significant, but it comes out with at least a trend toward a greater number in the low dose and a still greater number in the high-dose groups compared to placebo.

And I just would like you to comment on it. It's discordant from the other analyses and why is it discordant? And should we pay attention to it or why shouldn't we pay to it?

DR. KITT: Yes. I'm going to bring Dr. Todd Lorenz up to answer it, but while he's coming up, the serious adverse events were using a specific case report form page, to begin with, compared to the collection of

other data within the case report forms.

DR. LORENZ: There is a regulatory requirement with a definition for serious adverse events that is required by the regulations. What we did was use an algorithm that combined if it was either major bleeding or if an investigator had thought it was severe or if a patient had received a transfusion, and that's where the numbers that you're looking at come from. It's specifically a regulatory requirement and wasn't really a prespecified safety analysis.

DR. KONSTAM: Maybe you can't answer. Maybe this is really for the committee, but I guess I had a small question which was the technical question and I sort of knew the answer to it. You confirmed it. But I guess the other question is how much weight should we place on it, and maybe that's more for the committee than for you. But I just wanted to give you an opportunity to comment on it.

Again, it looks a little worse than the other prespecified analyses, and I just wonder if you have some explanation for it that could make us pay less attention to it, if you want to.

DR. LORENZ: Well, we don't contend that there's no effect of Integrilin on bleeding. We clearly showed an increase in minor events, and I think that in

general that should win your consideration.

But I'd like to ask Dr. Jimmy Tcheng to speak to the committee as well.

DR. TCHENG: I'm Dr. James Tcheng from Duke University.

I think in direct response to your question regarding the data that you're looking at in that specific table, that data is COSTART coding which includes any investigator-reported bleeding per the case report form for the CRF. The bleeding that was reported by investigators tended to include anything that was observed. As Dr. Lorenz has shown, there was an increase in what was considered to be objectively minor bleeding that was observed by the investigators.

The important relevant point here is that from a major bleeding criteria as applied by the TIMI group where we feel that these events represent serious clinical sequelae, there really was no difference from one group to the other.

DR. KONSTAM: Yes. It is referred to as serious bleeding in the adverse event reporting, so that required some judgment on the part of the investigators that it was serious by less defined criteria than the TIMI.

DR. TCHENG: That's correct. We used two

different criteria to describe bleeding. There was the major and the minor bleeding by the TIMI criteria. That was specified in the protocol as our primary safety endpoint. Then we also asked the investigators for an assessment, and that was graded as serious or insignificant bleeding.

DR. KONSTAM: Are these differences in the adverse event reportings statistically significant or not -- what's called serious bleeding as reported by the investigator? Do we know?

DR. TCHENG: We do not know the answer to that.

DR. KONSTAM: Okay. I think my last question is again related to the bleeding, and it relates to the interplay between bypass surgery and bleeding specifically. A certain number of the serious bleeding events occurred in patients undergoing bypass surgery, and the incidence of bypass surgery was greater in the placebo group. So, this sort of subjected the placebo group to another source of bleeding to a greater extent than the ones who had Integrilin, which is good, but it sort of was a little balancing act.

I guess there are different ways of looking at it, but I just wondered if you could comment on the whole issue.

DR. LORENZ: Sure. May I first have carrousel 6, slide 16 and then carrousel 6, slide 17?

This is the incidence of major bleeding in patients who do not undergo coronary artery bypass graft surgery. It's a subset analysis of major bleeding and contains approximately half of the number of patients who have major bleeding compared to the overall analysis. There is a small increase in the Integrilin-treated groups here compared to placebo.

May I have the next slide, major bleeding with coronary artery bypass graft surgery?

This demonstrates the incidence of major bleeding in patients who underwent coronary artery bypass graft surgery. Again, in this we saw a lower incidence of bleeding in patients who received Integrilin. I would point out that coronary artery bypass graft surgery actually is a risk factor for bleeding, and since there were fewer patients in the Integrilin-treated group who underwent that, in the overall results major bleeding came out identical across the treatment groups.

DR. KONSTAM: Well, I guess just to comment on it for my sake, I think there are two different ways of looking at it. One way is that if you prevent CABGs, that's a good thing, and so it doesn't really matter that

the number of bleeds in the non-CABG patients were higher in the Integrilin groups. And I have a lot of sympathy for that viewpoint.

However, the only reason I wanted to bring it up is it's a little bit different from the sort of impression that the data regarding serious bleeding gives at first blush that you just don't have to worry about it, that this difference in the CABGs does come into play as a reason. I think as clinicians begin to use Integrilin, I'm just concerned about the message that might come out that Integrilin does not predispose to increased serious bleeding. I'm not convinced of that because of this difference.

Does that make sense?

DR. LORENZ: Well, I think so, but the simplest analysis, of course, is all patients undergoing treatment in the trial and that's the analysis that we presented as just the simple default analysis.

DR. MASSIE: We have to move on a little bit from the bleeding point. We have an hour and 15 minutes left in this entire discussion.

DR. KONSTAM: Well, I'm through.

DR. MASSIE: Let's start down there and move it

this way.

DR. THADANI: A couple of questions. Since one of the endpoints is myocardial infarction not on Q-waves but also on enzymes and you're determining 30-day mortality as your composite endpoint at 30 days, how often did you do the enzyme? Did you do it every day? Because that becomes a softer endpoint if you did not.

DR. KITT: The enzymes were drawn in the study at baseline, 6 hours, 12 hours, and 24 hours.

DR. THADANI: What about afterwards?

DR. KITT: Actually the mean time in hospital was only 2 days in the study, so the patient would have those three determinations plus a determination at discharge. As I say, most patients were gone from the hospital at that time.

DR. THADANI: One of the difficult issues I always have is this because you're measuring -- one is the clinical infarct. The patient has chest pain. Another one is silent MI. I realize post-procedure you're doing tests, but if you're not doing serial tests, there's no way of knowing how many patients could have a silent infarction without Q-waves because I presume your definition of infarction on enzymes is based on what? Twice normal, three times normal?

DR. KITT: Three times normal after the procedure.

DR. THADANI: Just a CKMB or?

DR. KITT: We were looking for predominantly CKMB data, although in some institutions we only had CK.

DR. THADANI: The reason I'm saying that now, we know that the thrombonin-T probably is more sensitive sometimes. So, it becomes a softer endpoint.

DR. KITT: Sure.

DR. THADANI: That's one of the concerns that I have.

If you look at your other database, looking at death rate, it's very low.

DR. KITT: Yes.

DR. THADANI: So, I think one is relying a lot of database noise on infarct to a certain extent, which again you lose from the analysis I've seen at 30 days, .42 according to the FDA analysis which is outside your pre-required .035. So, that's the issue and some of the problems.

DR. KITT: I'd like to invite one of my clinical colleagues up, but before I do, I do want to point out that at the 30-day analysis, patients were also to have a repeat electrocardiogram and a thorough history and

physical examination such that if there were a silent MI that resulted in a Q-wave MI, we would have picked that up.

I also want to point out that the definition of myocardial infarction that we did use in the study was significant. It was three times the upper limit of normal in the study.

I would like to bring up one of my clinical colleagues to discuss the significance of that.

DR. THADANI: I'm not taking issue with the three times earlier phase, but I think if you got a 30-day endpoint, all of us know Q-wave infarction, yes, but you're going to miss out so-called non-Q-wave infarctions, so-called silent occlusions, first PTCA. So, it becomes a difficult evaluation for me because all your database is driven -- your need for revascularization is only -- urgent CABGs, 2 percent, 1 percent. Death is .1 percent, .01 percent, and very low even at 30 days. So, I'm just leery on that.

DR. MASSIE: As you bring up your clinical colleague, could you also give us the statistics on plain Q-wave MIs at 30 days?

DR. KITT: Sure.

DR. LINDENFELD: And just as part of that, what percentage of the total MIs were just enzyme MIs versus

clinically detected MIs?

DR. HARRINGTON: I'll cover all of that.

DR. MASSIE: Please and do it fairly quickly.

DR. HARRINGTON: Sure. Robert Harrington from Duke University.

The question as to the rigor of the endpoint I think is an important one not only in interventional clinical trials, but in interventional practice. In interventional practice, it is not typical to measure enzymes around the time of the interventional procedure. In fact, in a lot of clinical databases, the overall incidence of myocardial infarction is probably underestimated in a routine clinical practice.

In this study and in other studies that our group has done in the interventional population and in other populations of acute ischemic disease patients undergoing procedures, we've found that the rigor of checking systematic enzymes at predefined time points allows us to capture all of the myocardial infarctions that we feel are important.

Additionally, those ones where we capture were not determined by the clinical investigator. So, those ones came to bear mainly because of their enzyme criteria and not because of the clinical investigator saying, hey,

this patient had a myocardial infarction.

We have data now from seven randomized trials and observational databases showing that the appearance of CKMB at a level of three times the upper limit of normal is predictive of bad outcomes, not only at 30 days but at 6 months and beyond. So, I think that the rigor of the endpoint is actually a pretty good one especially considered against normal routine practice.

DR. MASSIE: Q-waves, Q-wave infarcts?

DR. KITT: It's actually on page 65 of the medical reviewer's comments at the bottom of the table at 30 days with print that I can barely see. Q-wave alone, 1.3 percent in the placebo group, .9 in the .5 microgram dose, and .1 in the Integrilin .75 group, p value .3 and .5.

DR. MASSIE: I was a little confused by this. There's 17, 12, and 13.

DR. KITT: Yes.

DR. MASSIE: But one is 10 times as high a percent as the other.

DR. KITT: I'm sorry. I didn't hear that.

DR. MASSIE: The 17 is 1.3 percent. 13 is only .1 percent. How can that --

DR. RODEN: It's 1 percent.

PARTICIPANT: Which page are you reading?

DR. MASSIE: I'm looking at Q-wave MI --

DR. KITT: Yes. That must be a mistake. That must be 1 percent.

DR. MASSIE: It must be 1.1 I would think.

DR. KITT: That must be 1 percent.

DR. MASSIE: All right.

DR. THADANI: You're saying most of the infarcts are enzyme determined up to 48 hours.

DR. KITT: Yes.

DR. THADANI: And yet, your composite prerequisite was 30 days.

DR. KITT: Yes.

DR. MASSIE: Yes, John?

DR. DiMARCO: I have two questions. One is, was any of the enzymatic data available to the investigators? In other words, the enzymes that you drew at 4 and 12 hours, were those reports given to the investigator and could they react, so the fact that you drew extra enzymes may have increased the reporting of clinical events?

DR. KITT: Yes, this was routine clinical practice. The CKs that are in here are what the investigator saw.

DR. DiMARCO: I know this is probably hard for you to answer. Since most of your events are enzymatically defined myocardial infarctions, is there any possibility that you would have missed enzymatically defined myocardial infarctions that occurred after that 24-hour time point and maybe happened between 48 and whenever?

DR. KITT: One thing that we did not describe either in my presentation and I don't believe it's extensively described in the material that you have is the procedures of the independent Clinical Events Committee who were extremely thorough in collecting any hint of repeat hospitalization, prolonged hospitalization. In fact, any CK value that was found in the chart was considered in the determination of whether a patient had a myocardial infarction. So, that process was extremely thorough.

DR. DiMARCO: But that doesn't answer the question. If these events were clinically silent, then they wouldn't have been rehospitalized. My understanding, at least in one of the tables, is there was a slight increase of about 1.5 percent of rehospitalization in the Integrilin groups.

DR. KITT: That's correct. You're absolutely correct with what you're saying, that if it was silent and there were no enzymes drawn, we would not have seen them.

DR. MASSIE: I have two questions.

The first one is, understanding the biology and the rationale, I'm having a little trouble deciding why the high dose didn't do at least as well, if not better, than the low dose. Is that a play of chance, or do you think that that's significant?

DR. KITT: Well, first, the two Integrilin dosing regimens had a common bolus dose, and the events, as you saw, occurred predominantly at the time of device deployment. So, the expectation was that this high dose, 135 microgram per kilo, would cover that period and in fact we'd have a common or a similar result in those two groups.

At the time of the IMPACT II study design, we had just completed this high/low study, and we had data available to us that bleeding was potentially going to be a major problem in this study. Therefore, our choice of two doses really was exploring a fair amount on the safety side. Therefore, the two different continuous infusions were really looking at exploring this differential safety effect.

Again, in the material that you were sent, there are descriptions of the results of that high/low study showing a fair amount of overlap in those two dosing regimens and that the bolus dose was in fact responsible

for the major effect in reducing the ischemic events.

DR. MASSIE: Well, that does bring two further questions. I guess the first one is, of course, we have to recommend one dose if we approve, and would that mean that we would recommend the low dose? Is that what you're requesting?

DR. KITT: That's correct.

DR. MASSIE: The second is there was a lot of discussion of replication during the presentation, but it would seem to me that the fact that the primary endpoint was barely hit in one and not replicated by the other dose is the most important example of nonreplication. Do you have any comments on that?

DR. KITT: Sure. The results of the primary endpoint, as you just mentioned, were positive, but it's really looking at where the effect was expected that we're asking you to consider in your --

DR. MASSIE: I understand that. I heard your elegant discussion of why we should be expecting it early and not seeing it late.

Although I don't like to hang too much on p values, you hit a primary endpoint and therefore you're asking us to look at a lot of these other endpoints perhaps, looking at it that way. But it seems to me that

our level of confidence that you with that low dose would hit a primary endpoint again is shaken by the fact that you didn't hit it with the other dose.

DR. KITT: Again, if you would allow me, I could describe looking at the Kaplan-Meier curves over time, particularly looking at the time periods up to 48 hours to 30 days and then also to 6 months looking at death and MI. The effect of both of those dosing regimens are almost overlapping. One place where they don't overlap actually is at 30 days.

DR. MASSIE: Well, that leads to my final question. Ordinarily this committee looks for two corroborating trials in trying to approve a drug for a specific indication and they should be showing important clinical endpoints. There have been exceptions, of course, when the endpoint is considered profoundly clinically important or when perhaps the endpoint is moderately important but the trial is so overwhelmingly positive that one might feel that way nonetheless.

There is no other trial in this particular indication.

DR. KITT: There are two additional studies. There was the first IMPACT study, 150 patients, which showed an effect. In that study the incidence of the

exact, same endpoint, death, MI, or urgent intervention, was 12 percent which was very similar to what we saw here. And in the longer infusion regimen, different doses but somewhat similar, the effect was about 4 or 5 percent in the Integrilin-treated groups. We actually provided the pooled analysis in the briefing document, and that p value also is .036. But we were not providing that as primary evidence but just corroborating evidence of that same effect.

DR. MASSIE: That is obviously the second question we have to consider whether if the first trial is deemed positive, but whether it's persuasive enough as a single trial.

I guess to me an overwhelmingly positive study would be a significant decrease in death and Q-wave myocardial infarction. Although enzymes I realize carry some poorer prognostic information, they're certainly not in the same sense irreversible. My numbers for that are 2 percent in the high dose, 1.4 percent in the low dose, and 2.4 percent in the high dose for death and Q-wave infarction, adding up that table.

So, I guess I must say I'm not blown away that this is a clinically overwhelming endpoint which would not make it unethical to replicate in another trial.

DR. KITT: Sure. Can I just comment on the significance of the myocardial infarctions that we had in the study? And I'd like to invite Dr. Harrington to speak.

But I also want to add that this is a very large study. There were 1,300 patients in each dosing arm that were replicating this result albeit not at the primary endpoint, but at all of the other endpoints that were significant for the antithrombotic effect.

But I'd like to bring Dr. Harrington up to describe the enzymatic infarctions.

DR. HARRINGTON: I want to actually respectfully but very strongly disagree with your statement that these enzyme elevations post-procedure are not important. The majority of events, as you know, that occur following intervention are not deaths, are not Q-wave myocardial infarction. Actually the incidence of those is very low in this population, and trials to show a positive effect on that endpoint would be, as you are well aware, quite large.

There's now, I believe, an overwhelming amount of data from a number of randomized trials that I could list for you, a number of single-center observational studies that have shown the clear-cut importance of the so-called mid-range enzyme bumps. There's an article in last

week's Journal of the American Medical Association from Charlie Davidson at the Northwestern Group showing the long-term implications of these mid-range enzyme bumps. There's a nice review, an editorial, by Eric Topol and Adelimeqid in December circulation showing again from the Cleveland clinical experience of over 4,000 patients with systematic enzymes long-term prognostic implications of the event.

So, I definitely agree with you, death, Q-wave MI, bad things in the interventional population. They're also very rare. These so-called mid-range enzyme bumps are not rare and they're very important. They're important at 30 days. They're important at 6 months. They're important at a year. So, that's the different opinion here.

DR. LINDENFELD: Were enzymes routinely measured at 48 hours?

DR. HARRINGTON: Most of the patients were no longer in the hospital at 48 hours.

DR. LINDENFELD: Because this was a 24-hour infusion.

DR. HARRINGTON: This was a 24-hour infusion.

DR. LINDENFELD: So, if there was a sudden reversal of effect and there are no enzymes at 48 hours, that might be the time we would expect to see enzyme

events. So, we have no way of estimating that effect.

DR. HARRINGTON: You're absolutely correct. There's no way of telling what happened after 48 hours.

Let me say, though, that in all the studies of abrupt closure, of all the studies of the acute ischemic complications of angioplasty, the randomized trials, the observational database, including our very own large database at Duke, the preponderance of these events, 80-85 percent of these events, occur in the very immediate peri-procedural period.

The investigator had the option to draw additional enzymes if there was a suspected event, funny chest pain, and the blinded, independent Clinical Events Committee took into consideration each and every one of those additional enzyme draws. So, it wasn't limited to those just around the procedure, but any else that were obtained. As Dr. Kitt pointed out, in contemporary angioplasty practice, the vast majority of these patients have gone home the next day, and that was in keeping with this study.

DR. LINDENFELD: But we have no enzymes following the cessation of the drug, routine enzyme draws.

DR. HARRINGTON: That's not true. We have it at 24 hours.

DR. LINDENFELD: 20 to 24?

DR. HARRINGTON: 20 to 22 hours, and the anti-platelet effect was gone by 24 hours.

DR. MASSIE: Do you have any other questions?

DR. LINDENFELD: I just have a quick one. Maybe you can help my confusion.

On table 513 on page 48 of the FDA document, I'm just concerned it says that when it classifies patient according to risk for the study under CRF risk classification, 35 percent of the patients were unstable angina, and then down below it says 68, almost 69 percent. Now, it says that was because between randomization and study, they might have changed, but I can't imagine 30 percent changed. Can you explain that?

DR. KITT: Sure. Actually we captured risk in the study in several ways. One way of asking that question is when the investigator called the randomization center, they were asked the question, is this patient having an acute myocardial infarction or unstable angina with the following definitions, and the definition was ECG changes and a relatively short time for -- I believe it was 24 hours.

The reason for revascularization, which is what you're seeing at the bottom of that page, the investigator

was asked -- the reason this patient is in the hospital and they actually had their procedure -- many of these patients actually were in for unstable angina, had an evaluation, were cooled off, so to speak, and then went on to have their procedure. So, they did not meet the unstable angina definition that would make them high risk for the risk stratification, but it was the reason that the investigator said that they actually performed the procedure.

DR. LINDENFELD: It's just a big difference from 35 percent to nearly 70.

DR. MOYE: I just have three questions I'd like to ask crisply in the interest of time.

The p value you report for the primary endpoint from what looks like a proportional hazards regression model is .035. Yet, I see in the FDA book it says .041. Is that a discrepancy that we can resolve quickly here or is that going to be a problem?

DR. KITT: I hope so. Dr. Kerry Lee I believe can answer that.

DR. LEE: The p value of .041 reported in the review by the FDA statistician was based on a different statistical test, different comparison that was used in the results that have previously been reported. That was based on the use of so-called exact statistics, whereas the

primary p value of .035 that Dr. Kitt has reported was based on conventional likelihood ratio chi square statistic. So, it's just a different approach.

I think in this particular study, the FDA reviewer was looking also, in addition to the composite endpoint, at some of the individual components where the numbers of events become somewhat smaller, but for the overall comparison of the primary endpoint, there are nearly 400 events, over 100 events in each of the treatment arms, and I think there's no problem actually with the validity of the properties of the more conventional statistics that were used. In fact, as you've pointed out, the logrank test, the Wilcoxon test looking at time-to-event data produced p values of .034.

DR. MOYE: Now, let me ask you. You came in right on the cusp because you were prespecified at .035 and in fact that's where you are. But I don't see where you adjusted for the DSMB's interim evaluations because there were, if I read this correctly, four of those and they involved examination of treatment differences in efficacy. Presumably the decisions made to continue the trial led to alpha expenditure and that should reduce the amount of alpha you have to spend at the end from .035 to a lower level. Do you disagree with that?

DR. LEE: You're absolutely correct about the interim analyses. There were four occasions when the committee had information to review. The O'Brien-Fleming type boundaries that were provided to them to use as a guide for interpreting the degree of significance at those interim evaluations of the data were structured in such a way that the final analysis could be performed at the .035 level.

Now, the point I would make once again, however, is that the .035, even accounting for these additional adjustments for the interim analyses, does indeed protect us from having a type 1 error probability that exceeds 5 percent for each of those evaluations.

DR. MOYE: Let me see if I understand what you said. Even though you had .035 in the beginning and you spent .035 in the end, you're not spending alpha at each of the individual looks. Is that right? Are you saying that the O'Brien-Fleming was constructed so that you would have .035 to spend at the end?

DR. LEE: That's correct, yes.

DR. MOYE: So, what did you spend initially?

DR. LEE: Well, if you look then at the effect of those adjustments on this .035 level of significance, actually for that comparison it would be slightly higher

than .035, but the final comparison at the final analysis was based on an .035 level so that hitting that would represent a significant result.

DR. MOYE: I'm not sure I'm with you, but why don't we go ahead.

DR. MASSIE: Mike, Cynthia?

DR. RAEHL: A quick question and then one pharmacodynamic question.

Was the combined pooling of the two dosage arms a prespecified analysis?

DR. KITT: No, they were not.

DR. RAEHL: It was not? Okay.

The second question is if one only administered the bolus dose of 135 mics per kilogram, what would be the expected physiologic time of that event? In other words, if you did not give the follow-up infusion, when would it be reversible?

DR. KITT: Integrilin is rapidly acting and in every study we've done, I believe the earliest time point we've measured is 5 minutes we've seen the maximum effect of a bolus dose. In the high/low study, certainly at 15 minutes we've seen maximum effect at the first time point at 15 minutes. Is that the question you're asking?

DR. RAEHL: I think so.

Then to Dr. Massie, the questions you were proposing earlier which were answered regarding the commonality was the bolus dose and how that basically evened the playing field between the two arms would suggest that the events would have had to occur within about a 15-30 minute time event to explain the difference between the dosage regimens. Does that make sense?

In other words, I can't explain the pharmacodynamic difference in relationship to the events. It doesn't make sense.

DR. KITT: Let me show you some of the results from the IMPACT high/low study to show you where we are in the inhibition of platelet aggregation.

DR. MASSIE: I'm just trying to figure. We have to conserve our time a little bit.

DR. RAEHL: I'll withhold it and ponder it.

DR. MASSIE: I'm just not sure how important that is in terms of the time course because it's very hard to, actually, read between the two groups. Not only were the boluses the same, but the actual dosing was very similar as well which is actually the cause of my concern, that they're not replicable because I really think you had two groups that were virtually identical and you got two different results. It's a little disconcerting.

DR. KITT: Actually on page 39 of your briefing document, figure 8-1 has that information.

DR. MASSIE: Dan?

DR. RODEN: Just to continue along the same lines for a second, if you look at your figure 16 or your slide 16 -- I think it's your slide 16, or this slide here, the time-to-first-event curves, those don't diverge until about 2 hours after the start of the drug. I think that's what we're having trouble with because if in fact this is a potent and immediate-onset platelet inhibitor, how do you explain that?

DR. KITT: Let me describe how the timing was done. It's actually a very important question.

The Clinical Events Committee were asked actually to time the events and what they used for the timing was the sample that they received from the lab for the CK elevation. That's what was called the time. So, in fact, when the actual event occurred one could only assume was exactly when they blew up the balloon. What you're seeing as measurement of time is our best ability to actually capture that with CK draws that were done during that study.

Dr. Tcheng, could you comment on that?

DR. RODEN: Can I ask another question?

DR. MASSIE: Yes.

DR. RODEN: You touched on the issue of the fact that there were randomized patients who ended up not getting the drug. Can you just review that for me again in 30 seconds and answer the question, which I presume you've thought about, whether there's a difference in the outcomes if you use a truly intention-to-treat analysis?

DR. KITT: Well, to answer the second part of your question, using every patient, all 4,010 patients, the difference is slightly different as described in the briefing book, but they are very, very similar.

Could I have carrousel 5, number 1?

While that's coming up, there were 139 patients that were not treated in the study. This study was well blinded with little ability for investigators to unblind or guess what the study drug was, and the reasons for not being treated in the study were predominantly due to the fact that when the patient got to the cath lab, the situation had changed. The lesion that was viewed in the cath lab was slightly different than the lesion that was viewed either 24 or 48 hours earlier or by the referring physician.

These are the results of the treated versus randomized patient analysis, and basically what you see is

a difference, first of all, in the placebo group, 11.4 to 11.6; 9.2, 9.1 in the .5 group; 9.9, 10.0 in the .75 group. Very small differences accounted for by this 139 patients.

DR. RODEN: That's fine.

Then can you talk to me a little bit about the doses again? I recognize that with a compound like this, it's not possible to define minimal effective and maximally tolerated doses and all that, unless you do these trials over and over and over again.

But it does bother me that you have this low dose/high dose issue and it bothers me as a pharmacologist that the low dose effect is higher than the high dose effect. I can't put it any better or more specifically than that except to ask you to talk to that a little bit more.

DR. KITT: Sure. The best evidence I have that these doses really are similar is the Kaplan-Meier curve that actually you just showed to me at 48 hours where the doses really are no different at all at the end of 48 hours. At the fifth day, the effect of both doses were identical, and after the fifth day, there were 29 additional events. Unfortunately, 14 of them were in that .75 group, 7 were in the .5 group, and 8 were in the placebo group. These events were all happening long after

the infusion was terminated, in this case 4 days after the infusion was terminated. So, we really do believe that that differential effect was a play of chance.

DR. RODEN: Just one final question. Can you summarize briefly, because I think Barry has touched on this as well, the outcome if you do the analysis using what I would call harder endpoints and that is death, Q-wave myocardial infarction, and not including what you and your colleagues have called enzyme bumps. If you could take out the bumps, how do the statistics come out?

DR. KITT: Well, I could tell you without looking at the numbers, it's not statistically significant. I don't have these at my fingertips. I know they are in that document that we were looking at a little while ago, the FDA medical reviewer's results, and those are all in there with the associated p values.

DR. MASSIE: Let me just ask the FDA reviewers whether you have any comments or questions you'd like to ask.

DR. TALARICO: We didn't know what to make of the fact that the two doses were not resulting in results -- did not provide data which were exactly similar, and if the two doses represented two replicative studies, the second study did not support the first study.

I had some question with actually the true dosage of the drug because in some patients the platelet aggregation was assessed at the end of treatment and the initially aimed-at platelet inhibition of aggregation of 80 percent was actually achieved in about 40 percent only of patients. So, whether we are dealing here with inadequate treatment, had the treatment been higher or longer, could we have had a stronger result.

The other issue which I thought was very important was the bleeding, which has been talked about before. I have a great problem assessing really what bleeding is from studies because the definition of bleeding is quite different, and I have reached the conclusion that bleeding is under-reported in most of the studies. Therefore, if an investigator is impressed by the bleeding, I tended to believe the investigator rather than the adjudicating committee who probably has only less data available.

The safety of the drug was quite satisfactory in the things there were major problems with, but there was some bleeding difference from placebo. These were patients who were challenged with femoral arterial lines. Therefore they had the site from where bleeding could easily be assessed, and there was some difference. So, I don't know

whether it is in the dose could have resulted in better efficacy without paying with more bleeding.

The other issue which has been mentioned and I would like to clarify, the bleeding within CABG and non-CABG patients. Integrilin does have an antithrombotic effect as well, besides the anti-platelet, because if you affect the platelet membrane, you affect the lipid substrate on which thrombin can be generated. So, some of these patients, actually the patients who did undergo PTCA had less happening than the group of placebo patients. So, that might have also explained in part why there was a difference within CABG and non-CABG patients.

DR. MASSIE: Thank you for those comments.

DR. SANKOH: Abdul Sankoh, the statistician for the FDA.

I just wanted to explain one of the issues reached by one of the gentlemen regarding the use of the alpha level and still ending with the same alpha level. So, you spend it and it doesn't seem to go away.

I think what happens here, there were two types of interim analyses that were done. An interim analysis for re-estimation of the sample size was done, and an interim analysis for efficacy was done, although it was not stated in the protocol.

So, what happens, they were eating the alpha as they were going along, but they keep increasing the power because they re-estimated the sample size. So, because you maintain the power you started with, you keep the same type 2 error, and as long as the type 2 error is not increasing, your alpha level in the beginning, the type 1, stays the same because there is a relationship between the type 1 and the type 2 error. As long as you maintain the power, it seems like you're not eating your alpha but you are, but as you eat it, you increase the power, you maintain it there.

So, that what happens there. That's why you didn't see it going anywhere because the trial was sized for 3,500 and it ended up with 4,100. So, basically that's why you're not seeing it there.

DR. MOYE: I would say that that is very imaginative.

(Laughter.)

DR. THADANI: Barry, before you start the questions, one burning question I have is you tried to allude from the discussions that silent bump with enzymes has prognostic significance. I'm not denying that, but in your database it doesn't show up. You've got several thousand patients, and when I look at it, the event rate, death is only 1.1 percent in placebo, and .9, and high dose

.5.

So, although I buy what the literature says, it's not given in this database. So, I'm not denying. I read the CPK. I read the thrombonin-T results, yes, but in the given database I cannot conclude that your presumption that silent bump in enzymes CPK-wise has been reflected at least in real terms. I know there's a .5 percent difference, but I'm not convinced.

DR. TCHENG: This is James Tcheng again from Duke.

Let me try to address the question that you're asking from just a little bit different perspective, but specifically looking at the prognostic significance of MBCK elevation in the IMPACT II population, if I could have slide number 46.

Again, the important thing to remember is that we in the protocol specified that everybody would receive an MBCK assessment at 6 hours, 12 hours, and 24 hours, and then per the investigator's discretion after that if there was a clinically relevant event.

The slide that I'm showing here is a correlation of 30-day outcome. This is a composite of death, a second myocardial infarction, or urgent intervention correlated by the peri-procedural rise in

MBCK. Here you see 0 to 1 time. This is the 1 to 3 times which was not called infarction in the protocol, but I've shown the data here. This is the greater than 3 to 5 times, and again you can see the gradient here.

There clearly is a correlation with every component of the endpoint, death, myocardial infarction, bypass surgery, repeat intervention. You can see the effect here, the predictive value, if you will, of an MBCK elevation in the peri-procedural period.

If we can go to the next slide --

DR. THADANI: And between 3 and 10, there is no difference. Right? It's very flat. The last slide, the one you showed before.

DR. TCHENG: Can we go back to the previous slide please?

DR. THADANI: Looking at your 30-day.

DR. TCHENG: This is a 30-day --

DR. THADANI: Yes, there is no difference between 3 to 5 versus more than 10 times.

DR. TCHENG: 3 to 5 is shown here in this light purple, but there is a gradient here. You can see that it's greater than 10 times. If you add up the composite, this --

DR. THADANI: No, I understand that adding up,

but there's not much difference between 3 times versus 10 times.

DR. TCHENG: Yes, I would agree. In fact, most of the information is anything above 3 times.

DR. MASSIE: It's perhaps superfluous to point out the fact that the deaths and the MIs are included as endpoints.

DR. TCHENG: No, no. This is not a recursive analysis, if that's what you're indicating. In other words, this is just if somebody had a peri-procedural elevation of the MB, what happened in terms of --

DR. MASSIE: But if what happened was that they died or they had an infarct before 30 days, they are in the 30-day endpoint. Is that not true?

DR. TCHENG: It's a second event.

DR. MASSIE: It may be a second event, but they're in the endpoint, though, right?

DR. TCHENG: No. This is any elevation of MB as correlated with outcomes.

If I can go to the next slide please.

DR. RODEN: This is only patients who get an endpoint because of what you have been calling a bump, not patients who get an endpoint because they have a myocardial infarction.

DR. TCHENG: That's correct, yes.

This is the out-points to 6 months, and again you can see that the predictive value of elevations of even small amounts of MB -- here the 1 to 3 times in the dark purple. There's a doubling of the rate of a second myocardial infarction. There's almost a doubling of the rate of death and myocardial infarction if you even have a 1 to 3 times the upper limit of normal bump in your MB.

The only point it is not predictive of is the secondary angioplasty procedures.

DR. MASSIE: Interesting.

Okay, well, we're down to our nearly final 30 minutes. I think that Marv had another question.

DR. KONSTAM: No.

DR. HOMCY: I'm a little bit confused by the term and the implications of the term "bump." A threefold increase in CPKMB is a classic definition --

DR. RODEN: Then tell Dr. Harrington not to use that term.

(Laughter.)

DR. HOMCY: -- is a classic definition of an MI. Again, I don't know how CPKMB gets into the -- it's one of the criteria for calling an MI and I don't know how it gets into the serum without necrosis occurring, number

one.

And number two, in the principal investigator's call, which would be clinically relevant or clinically identified MIs, he saw the same reduction in same MIs that were called by the CEC.

So, however you cut this beast, you see the same sort of thing.

DR. THADANI: Nobody is cutting the pieces of the bumps. What we are questioning is if you did not measure routinely after 24 hours, how much you could have missed the silent bumps which could be equally important to determine your later death rate, MI. I think you don't have data to show that. That's the problem we're having because you stopped the infusion at 24 hours. There's no way of knowing because your whole database is driven by high infarct rate based on so-called bumps earlier on, and I'm suggesting that had you done a serial one -- I know it was not done -- it becomes a softer endpoint to me. I know silent occlusions occur, I know infarcts occur post-intervention which there is no way of getting to the data.

DR. HOMCY: I understand what you're saying, but I'd like to point out that there's an almost 8 percent rate of myocardial infarction in this study in elective patients.

DR. KONSTAM: The problem, Udho, is that if you stick to that, if you really don't believe that this is important -- I mean, discount that -- then you're stuck with saying that you have to do huge, huge trials in order to find the number of endpoints that you're going to want to show efficacy on that level. So, is that what you think?

DR. THADANI: No. Marvin, up to 24 hours I have no problem because the fact there is a catch-up phenomenon and you lose at 30 days, that means silent occlusions are occurring or something is going on to change the whole outcome. So, I'm not saying that there's no reason to believe the CPK arrives earlier on, and I think the guidelines demand that you have to do repeatedly three CPKs post-intervention, otherwise they question you why you didn't do it.

So, in a trial when you're looking at 30-day stuff, I think you're going to lose a lot of it because if you just base it on enzymes. So, I'm not saying that 24 hours is not important, but I think you could have missed events. Your death rate is slow low, 1.1. At 30 days to translate that into because the enzymes increase, I think I see all your points well taken. I have some problems with missing data points.

DR. MASSIE: I think, Marvin, the point is not that these aren't important and those data were very impressive, indeed. I guess the question that we're going to have to struggle with in a second that I was trying to bring up to get some feeling on how to answer it is whether this is such a powerful trial that we can take one trial to make a decision on. To me if they were infarcts that killed people or infarcts that were more familiar to me as being fatal, even though these are not non-serious, I'd be a little more convinced that this trial is powerful enough and important enough to do it based on one trial.

You've come back to haunt us.

(Laughter.)

DR. LIPICKY: I wanted to remind you that you should remember what the number .05 squared is. That is impressive.

DR. MASSIE: That is impressive. Is it remembering or relearning?

DR. LIPICKY: Well, just that you should remember an impressive number is .05 squared. That's the usual standard.

DR. MASSIE: On a very important clinical endpoint. Well, less important if it's .05 squared.

DR. LIPICKY: The less important or the less

convinced you are that you have a really meaningful endpoint, the more assurance you'd want to have I believe.

DR. MASSIE: Well, unlike our usual situation, we really have only three questions, and I don't want to read through all three of them. I want to just pick out the two that I think we are probably going to need to vote on.

The first is, does the IMPACT II study show a significant clinical benefit of Integrilin on acute ischemic events following PTCA or on its primary endpoint?

The second I think that we're going to need to look at is, since IMPACT II is the main support for the proposed indication, is that single study sufficiently persuasive to support approval?

And then the third we can discuss after we do the first two.

I think if there's not any further discussion, we should move on to the first question and have Marv lead off by discussing and then casting his vote I guess.

DR. KONSTAM: You want to take one question at a time?

DR. MASSIE: Yes.

DR. KONSTAM: And the second question is going to be, do we have enough with IMPACT II so that we don't

need a replicative trial?

DR. MASSIE: Right.

DR. KONSTAM: Or is there some replication?

DR. MASSIE: I think that's what they want. Unfortunately, Dr. Fred is not here to quite guide us through that, but I think that's fairly clearly stated in the question. Is that right?

DR. TALARICO: That's correct. We wanted you to consider supporting evidence like the IMPACT I trial, the size of the trial, and so forth, judge on all parameters whether one trial was going to be adequate, how convincing clinically, what's the clinical impact of the results.

DR. MASSIE: Then let me just rephrase that to say we'll vote secondly whether the single trial is persuasive enough and discuss whether there's additional data, if we say no that it isn't, that would make it persuasive enough. Then finally, I guess we need to bring up the unstable angina trial if we still are uncertain, which is the end of the second question. So, the first question, IMPACT II.

DR. KONSTAM: So, my feeling is we have a positive trial. It met its prespecified primary endpoint not by much, but I think it did.

I think that perhaps the investigators were a little unlucky in their particular choice because there were some other endpoints or time points that were a lot more obviously positive and were obviously positive in both groups.

I personally accept the primary endpoint that was chosen. I agree, it would have been nice to have an even more physiologically meaning endpoint, but I think this one is pretty good, and I think we have a positive trial.

DR. MASSIE: Does anybody else want to comment on that question before we all vote?

DR. THADANI: Barry, can I make a comment? I can't vote.

The fact the high dose did not work really concerns me. There's no way on earth that if it's blocking platelet effects you should not have seen much effect -- since the 30-day is the point, the high dose is not effective. So, I have a major problem to conclude that the trial if definitive. So, I think I want to raise that concern. I know Marvin --

DR. KONSTAM: Well, no, I mean --

DR. THADANI: But I think I got a major reservation.

DR. KONSTAM: Udho, the question I would have for you is whether that point says that this is not a positive trial.

DR. THADANI: Yes. The p value is .20 at high dose and low dose is .04. So, to me it's not convincing.

DR. KONSTAM: Right, but the issue there is whether the p of .035 on one of the two limbs is sufficient to call it a positive trial. My interpretation of all of the comments that we've had from the statisticians is that it is. I'm not sure Lem agrees with that, but my judgment is that it is a positive trial on the basis of one of the limbs reaching the .035.

DR. MOYE: I just say very briefly that the investigators prospectively said what their endpoint was and what the p value was, I mean barely, but they got there.

DR. KONSTAM: If they had said .1, that would have been all right?

DR. MOYE: .1? That's a different issue if they had said .1. I guess the issue is if they had .1, they reached it, but are we really going to accept a 10 percent alpha?

DR. KONSTAM: All right, but you accept the .035.

DR. MOYE: Yes.

DR. MASSIE: My interpretation of the higher dose is that it's probably just as good, but we're at the margins of power with the sample size and the event rate they saw and it didn't make it, which of course leaves one in a quandary as to what dose one would really recommend if we really don't think they're different. But in terms of the primary endpoint, it sounds like they did it right and they found it.

Do you want to go ahead and vote first? I know that was a vote yes. Say yes.

DR. KONSTAM: Yes.

DR. MASSIE: Dan?

DR. RODEN: Yes.

DR. RAEHL: I'm going to vote no. I'm not convinced. I think the low dose could be just as ineffective as the high dose and you had two arms.

DR. WEBER: I'm going to vote yes. I thought the low dose, as Dr. Moye just explained, got there, and the slightly higher dose was pointing in the same direction. It doesn't particularly bother me that there's a small difference between the doses. I think in fact the doses are virtually identical, and that there's a slight variation in what they achieved doesn't strike me as

particularly astonishing. The overall impression I'm left with is that this drug is different from placebo.

DR. MOYE: Yes.

DR. LINDENFELD: Yes, I agree.

DR. MASSIE: Yes.

DR. DiMARCO: I'm going to vote no. The reason is I think that I'm concerned that another group of the same size with a roughly similar infusion came out statistically off, so that I don't think it's what I'd call two studies, and if you combine them together, it's one study.

The question is worded "significant clinical benefit." As someone who refers people for this type of interventional procedure, I look at the total difference in event rate as essentially equal to what for me is significant bleeding complications, and so the risk-benefit ratio becomes a little questionable in my mind So, I'm going to vote no.

DR. MASSIE: 6-2 yes.

So, that means we need to go on to the second question which we've now defined as a several part question. I guess the first part of it is since IMPACT II is the main support for the proposed indication, is that single study sufficiently persuasive to support approval?

Marv, do you want to comment first?

DR. KONSTAM: I've been thinking about this, and I'm going to give my viewpoint and I'd actually like to hear what other people think of it before I actually cast my vote.

I think that we don't have replication, and so you'd have to look for some other reason to accept the findings without replication. Well, you might find some replication. You might say that the other limb of the trial, although it doesn't reach it, it's trending in the right direction and maybe that gives you some solace, but I guess there are some people who are actually dissuaded by that point.

The thing about this is I think that this drug is acting to me as an instrument to achieve a physiologic effect for which we have overwhelming evidence has benefit in terms of adverse events associated with angioplasty. I personally view that a little bit differently than I would if you were giving a drug that you really were unsure how it were acting and you were just focusing on the endpoint.

I guess I view it a little bit as an instrument drug. Maybe in my own mind I view an analogy of, let's say, you had a new catheter and that new catheter was shown to be associated with a reduction in acute closure in

association with angioplasty. Would you demand outcome information from that? I'm not sure whether you would or not. I personally would be more permissive in saying that I have an instrument. I sort of view this drug that way.

I think we have such an overwhelming amount of information of the adverse effect of platelet aggregation associated with angioplasty, and it seems pretty clear to me that this drug has precisely the effect that I want to achieve during the angioplasty and to my mind it does it better in at least some ways than anything else we have in this domain. I guess for whatever reason that set of arguments permits me in my own mind to be more permissive of not having confirmation from a second trial.

I don't know if that makes sense to anybody. I see Ray approaching the microphone.

(Laughter.)

DR. KONSTAM: But that's my thought.

DR. MASSIE: Ray?

DR. LIPICKY: Well, that makes sense. We frequently talk about things like that.

The problem is that it verges on the -- and I'll cite the extreme. Let me say I have a new chemical entity and very clearly demonstrate that it is an angiotensin converting enzyme inhibitor in vitro. Does

that mean it can be approved for hypertension?

DR. KONSTAM: Well, my answer to that --

DR. LIPICKY: It would be a tool. Right? And clearly you know the mechanism of action. You need to have something else, and approval generally rests upon having demonstrable clinical benefit with two exceptions -- and you guys were trying to wipe that out this morning -- namely, hypertension and angina.

(Laughter.)

DR. LIPICKY: So, I think that's an important thing to bear in mind, that approval depends upon having demonstrable clinical benefit where you believe that the evidence would suggest you can replicate that finding and not that the heart rate slows and that's good or that it's a platelet inhibitor and that's good.

DR. KONSTAM: Well, Ray, let me just ask, though. It's not we have no data here. We have a study that in fact the panel has voted is a clearly positive study. So, the question I would ask is --

DR. LIPICKY: Well, I would disagree with the panel. It's sort of borderline. Okay?

And not that it makes any difference whether it's positive or borderline or negative. It is not terribly convincing. I would probably say something

different if for Q-wave MI and death it had a p of .0001, but when it has a p of .034 with a prespecified need for .035 and it includes things that are not that hard, I would say, yes, that's a positive trial maybe.

But I don't feel compelled because I have said that to recommend its approval, and it's not infrequent that we will tell people they can use combined endpoints, have a positive trial in the sense of that binary counting, and not be approvable.

DR. MASSIE: Okay, I think we've heard. Does anybody else on the committee want to comment as Marv asked?

DR. THADANI: Yes. I think without a clinical endpoint, what can you rely on? You can blow the balloon up, you can put anything in that artery. If the artery doesn't stay open, our patient doesn't survive, what's the point? So, I have a major difference with what he said.

DR. TALARICO: Our question was how much clinical importance, how much clinical merit there is in a drug which has a very strong, acute, immediate effect. There's no question that in the first 48 hours, there's a marked difference. We can call it prevents abrupt closure. What does that mean clinically? If at 30 days the effect is not as we would have liked to see, but it's not

completely lost, how do we translate that in clinical merit?

DR. KONSTAM: Actually I construct that in my own mind very much as the sponsor said it, that I think that this is an important endpoint that is preventing acute reclosure, but I'd like to see it stick at 30 days or at 6 months or at some other time point, which is sort of the way I construct this frankly, as opposed to saying, aha, the primary endpoint is 30 days. I think that this drug has a dramatic acute effect and we see evidence that it's sustained at 30 days and 6 months.

DR. TALARICO: Yes. I would like to forget that the endpoint was 30 days. Let's say if you forget that it was pre-established at 30 days and you have this result, is it good to have much less abrupt closure within the first 48 hours and to carry some efficacy all along the curves and --

DR. KONSTAM: I would argue not unless you can convince yourself somehow that it is tending to be sustained. I would be concerned about the possibility, for example, that you could prevent acute reclosure but that you're preventing it in certain arteries that then are going to go ahead to be predisposed to close a few days later. But I don't think we see that here.

DR. MOYE: I guess my read of the trial is that it is statistically significant but of marginal clinical benefit. The major reason for that is what the investigators said initially. They were looking for a 30 percent reduction, and to me that means that they were saying that anything less than 30 percent wasn't worth detecting. So, you initially sized the trial so that when you get to 30 percent, you fall into the critical region and you reject the null hypothesis.

What's happened here is that they increased the sample size understandably and I think appropriately, but they increased the sample size and so they wound up with a test statistic falling in the critical region for a much lower efficacy, 22 percent efficacy. And in addition, you have the problem with the other dose not showing any efficacy at all. So, I think this is of limited clinical benefit.

DR. MASSIE: I guess I don't like to be totally bound and I'm sure Ray wouldn't bind me on this .0025, but I think the type of trial that I would be willing to accept as one positive trial enough to not restudy it would either be one that significantly reduced death perhaps by less than 30 percent or 20 percent or even 10 percent but at least that, and I think a clinical endpoint of death and

myocardial infarction Q-wave would satisfy me. I don't doubt that if I had an angioplasty, I wouldn't want a CK "bump," but I can't be quite as convinced that that's as important.

Or a trial that had a clinically relevant endpoint but the p value was so small, as Ray would say, that I was sure that if I did it again, it would happen again. Here we have some internal inconsistencies that are already pointed. I'm not sure that if we did this exact, same trial again, it would fall on the .034 side of the .035, and I don't think the clinical endpoint is that powerful to approve it based on one trial.

So, I think by both measures of why we usually require two positive trials with clinically important endpoints, I don't think that this one trial makes it although I think it's a positive trial and therefore a good down payment on a two-trial approval.

I don't know if there are any other comments before we vote.

DR. WEBER: Can Marvin respond to that?

DR. MASSIE: Yes, please.

DR. KONSTAM: I'd actually rather hear what other people say before I --

DR. MASSIE: Well, we can let you vote last.

DR. KONSTAM: Are we ready to vote?

DR. MASSIE: Nobody else said that they wanted to say anything.

DR. WEBER: Beyond your general hypothesis that we're dealing with a problem that's very much linked to platelets and that here is a well-designed, well-proven drug with an effect on platelets, so it meets your expectations and this adds support to what was in the study, were there any other lines of evidence that were presented by anecdote or by history that support this thinking or are we really just left with the summary that Barry gave us and your --

DR. KONSTAM: Well, I'm not sure what you're asking, Mike. I don't think that there's any doubt about the role of platelets in adverse events associated with angioplasty. I think that that's unquestioned.

I guess all I was saying, without quite committing yet how I was going to vote, that I'm very sympathetic to the view that if you really know an awful lot about the physiology at hand and you have a drug that is very clearly influencing that in a way that you want to without bad things happening, and then you have some significant endpoint support of that, I guess what I'm saying is I'd be more permissive of not absolutely sticking

to the usual criteria of two replicated primary endpoints in putting that together and saying I'd approve.

Now, I am at the same time influenced by what Ray said. I think I would stick very firmly to what I was saying I think if I was absolutely overwhelmed by this study, but I'm waffling because I'm not absolutely overwhelmed by this study. That's I guess where I'm coming down.

DR. RAEHL: Just a quick comment. I think it's a very dangerous precedent to take what we may agree to be a pathophysiologic mechanism of an agent and therefore make the jump that in practice that will be an efficacious drug because our role is to make sure that a drug, when it's approved, is both safe and efficacious, and I don't think we can step back from that despite what I would submit would be our uniform desire that this drug works.

DR. KONSTAM: I agree with that completely. I'm not suggesting approving this drug on the basis of its anti-platelet actions. Forget the problems with IMPACT II. Let's assume IMPACT II were overwhelmingly clear. I would take the stand that that, coupled with the concept that this is a drug doing precisely what we know influences pathophysiology, to me would simply sway me toward being permissive of backing off of the usual demand of replicated

trials.

DR. MASSIE: You can have one more comment and then we're going to have to --

DR. LINDENFELD: I agree with Marv. I think if this trial were overwhelmingly impressive, that given what we know, it would be enough.

DR. MASSIE: Marv, do you want to vote first or last?

DR. KONSTAM: Well, Ray has completely convinced me. I'm almost there but I guess I've got the two sets of problems. I think it's a positive trial, but based on the primary endpoint it's borderline. In the face of that, I guess I'm not willing to push to say I don't need replication based on what I said about physiology. So, I'm going to have to vote no.

DR. MASSIE: Dan?

DR. RODEN: No.

DR. RAEHL: No.

DR. WEBER: No. I'll vote no as well for the same reasons that Marvin put forward. But I guess if we're saying no now, we are acknowledging an important concept in a drug that potentially can meet that concept. We just need to know more about it.

DR. MOYE: Not sufficiently persuasive.

DR. LINDENFELD: No.

DR. MASSIE: No.

DR. DiMARCO: No. Again, I think you really need a very positive trial with very hard endpoints to break the standard of two trials.

DR. MASSIE: We have two other questions. One we didn't have a lot of discussion on. I think we all read the packet, but is there any other material that the sponsor has provided from the IMPACT I trial or the high/low dose trial that is sufficiently confirmatory to count as our second trial or to account as a substitute? In other words, is anybody convinced by it? Marvin? No?

DR. KONSTAM: Is the question, do we find supportive data in the --

DR. MASSIE: Right.

DR. KONSTAM: No, I don't see it.

DR. MASSIE: Finally, we come to -- well, not quite finally, but there's an unstable angina trial ongoing with Integrilin. I personally don't know much about it. I'm sure the sponsor can fill us in, but I guess the division is asking us how we would respond I guess in terms of the PTCA endpoint as a potential endpoint if there was a positive result for an unstable angina trial. Is that what you're asking us? Or if we had approved it, would we --

I'm sorry.

Would a negative result in this study affect our conclusion? Well, I think the answer is it obviously would not affect our conclusion.

But I guess probably a relevant question is the one I just asked. Would a trial for another indication with the same product allow you to broaden this indication? Do we want to discuss that question? Are you interested in our answer, or should we pass on that?

DR. TALARICO: We'd like you to discuss it.

DR. MASSIE: Ray?

DR. LIPICKY: I don't believe that you have been adequately prepared to discuss that and that whatever conclusion you would come to would be kind of off the top of the hat without having had the appropriate background. So, my preference would be that you would ignore that question.

DR. MASSIE: Okay, I think we can leave that question to another day I guess.

Then I think this meeting is adjourned.

(Whereupon, at 4:38 p.m., the committee was adjourned.)